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THE COMBINED EFFECT OF CORTISONE AND PARTIAL PROTEIN DEPLETION ON WOUND HEALING*

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MANY investigators have reported retardation of wound healing by cortisone or ACTH.[1-7] They have noted the depressant action on many phases of healing, including vascular growth, fibroplasia and the deposition of normally staining extracellular material. Relative absence of the inflammatory elements but only slight slowing of epithelization has also been observed. These observations were made on different laboratory animals, using different methods of wounding.

There have been, however, several clinical reports on patients with burns and surgical wounds that healed normally in the presence of ACTH or cortisone administration.[8-13] Some have attributed this difference to inadequate or too infrequent administration of the drugs. On the other hand, laboratory investigators have been criticized for giving toxic doses of cortisone and ACTH. However, the first reports on failure of healing were made clinically by Ragan with nontoxic doses of ACTH.[14] His patients were very ill and ran high fevers.

It is our contention that the nutritional state is an important factor that contributes to the failure of healing and that in inadequately nourished persons a smaller than usual quantity of cortisone or ACTH may be effective. Evidence will be presented to show that a nontoxic dose of cortisone interferes with healing in animals that are partially depleted in respect to protein.

How much a rabbit can be deprived of protein before healing is delayed and what happens to weight and circulating blood constituents were first determined in order to establish criteria for the selection of animals to be used in the second portion of the investigation.

Adult rabbits weighing between 2.5 and 3.0 kg. were placed in wire-floored cages and given water *ad libitum* throughout the experiment. They were given no food for a week, after which they were fed a synthetic diet containing less than 1 per cent protein and consisting of dextrin 45 per cent, lard 15 per cent, cellulose 24 per cent, Osborn and Mendel salt mixture 4 per cent, manganese sulfate 0.1 per cent, calcium propionate 0.1 per cent, dried yeast 10 per cent, oleopercomorphum 1.0 per cent and Lederplex vitamin mixture 0.5 per cent. One hundred milligrams of ascorbic acid was administered subcutaneously twice a week throughout the experiment. Weight charts were kept on all animals.

Heart-blood samples were taken before the animals were starved and at the time of wounding. Not more than 10 cc. of blood was removed at any one time. Gregerson's method was used to determine circulating red-cell mass and blood and plasma volumes.[15] The albumin and globulin concentrations in the serum were estimated by the technic of Wu.[16] From these findings total circulating albumin and globulin in the blood of each animal were calculated.

The rabbits were wounded at different stages of depletion, as outlined by Findlay and Howes.[17] This method utilizes an incised and sutured wound at the base and dorsum of the rabbit's ear. The rate of healing was measured by testing the tensile strength of the wound.

RESULTS

The values of the blood volumes and constituents at the start of the operation are given in Table 1. The percentage decrease of blood volumes and constituents correlated with weight loss are shown numerically in Table 2. The decrease in total circulating albumin is shown graphically with the same correlation in Figure 1.

The decrease in the circulating red-cell mass and blood and plasma volumes plotted against weight loss did not follow a definite pattern. Total circulating albumin was found to decrease rapidly while the animal was losing 10 per cent of its weight, but it did not decrease significantly further until more than

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30 per cent weight loss was obtained. Therefore, animals losing between 10 and 30 per cent of their weight might be expected to have approximately the same depression of values for total circulating albumin.

Table 3 shows wound tensile strengths correlated with weight loss. Rabbits that lost from 3.1 to 19 per cent of their weight showed little change in the rate of wound healing. However, when the weight loss was from 25 to 35 per cent healing was significantly retarded. In other words, a protein-depleted rabbit must lose more than 20 per cent of its weight before healing is adversely affected. Conversely, wounds in rabbits that have lost less than 20 per cent heal at a normal rate. Total circulating-albumin determinations cannot be used to predict the manner and rate of healing.

TABLE 1. *Normal Values in Rabbits Weighing 2.46–3.65 Kg. (Average Weight, 2.85 Kg.).*

DETERMINATION	NO. OF ANIMALS STUDIED	RESULT	EXPRESSION OF VALUE	STANDARD DEVIATION
Serum albumin	19	5.59	Gm. per 100 cc.	σ0.51
Serum globulin	19	1.84	Gm. per 100 cc.	σ0.48
Blood volume	13	71.9	Cc./kg. animal weight	σ11.9
Plasma volume	13	44.5	Cc./kg. animal weight	σ6.9
Circulating red-cell mass	13	27.4	Cc./kg. animal weight	σ6.4
Total circulating albumin	10	7.41	Gm.	σ1.51
Total circulating globulin	10	2.47	Gm.	σ0.81

The second portion of the investigation was to determine the effect of cortisone on wounds in rabbits insufficiently depleted of protein to cause a definite delay in healing. To do this it was first necessary to find a dosage that would not seriously affect healing in a rabbit on a normal diet. Cortisone,* 1.5 mg. per kg. of body weight per day, given subcutaneously, was finally selected.

Animals were then divided into 5 groups and given the following experimental regimens: The first group was given a well balanced diet (Rockland Chow) containing approximately 18 per cent protein throughout the entire experiment. After a week of starvation, the second group was given the low-protein diet previously described until their weights were stabilized at less than 20 per cent loss. They were then operated on and continued on the diet postoperatively. The third group was treated as the second, except that a Rockland

*Supplied by Merck and Company, Incorporated, Rahway, New Jersey.

TABLE 2. *Decrease of Blood Volume and Blood Constituents With Loss of Weight.*

WEIGHT LOSS	BLOOD VOLUME	PLASMA VOLUME	RED-CELL MASS	ALBUMIN CONCENTRATION	TOTAL CIRCULATING ALBUMIN	GLOBULIN CONCENTRATION	TOTAL CIRCULATING GLOBULIN
%	%	%	%	%	%	%	%
3.1	18	12.6	26.0	+ 3.5	8.5	+16.6	+ 1.9
5.8	16.2	22.1	4.1	0	22.2	4	24.0
8.3	2.8	5.1	+0.8	32.7	36.7	+29.0	+21.0
11.6	10.4	5.0	19.4	32.2	36	+42.8	+31
19.5	23.2	18.3	29.5	31.0	43.9	+12.5	5.5
25.0	30.4	28.6	33.7	30	48.6	+15.4	24.1
25.0	20.3	18.0	24.0	33.3	45.7	+16.6	+15.8
29.8	26.0	29.4	18.0	19.0	42.7	0	29.4
39.0	35.7	35.3	36.8	18.2	48.3	+22.2	21.1
42.5	39.7	43.4	34.1	32.7	61.9	34.6	63.0

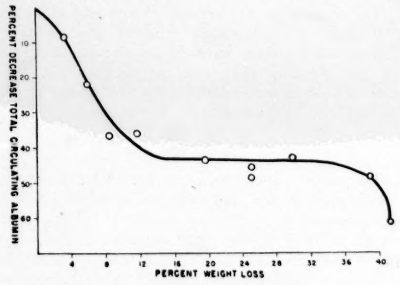

FIGURE 1. *Decrease of Total Circulating Albumin Correlated with Weight Loss.*

TABLE 3. *Wound Tensile Strengths in Rabbits on Low-Protein Diet, According to Weight Loss.*

LESS THAN 20 PER CENT WEIGHT LOSS		GREATER THAN 20 PER CENT WEIGHT LOSS	
WEIGHT LOSS	TENSILE STRENGTH	WEIGHT LOSS	TENSILE STRENGTH
%	%	%	%
3.1	195.4	25.0	55.7
8.3	133.2	29.1	111.6
11.6	163.3	32.0	60.4
19.0	161.3	35.0	62.7

Chow diet was given after operation. The fourth group was treated as the second, with the addition of cortisone from the day of operation until they were killed. The last group was allowed to lose less than 20 per cent weight preoperatively on the low-protein diet. At the time of surgery cortisone was started and the animals were given a Rockland Chow diet *ad libitum* after operation.

All weight changes in each animal were charted daily during the period of observation and treatment. The daily food intake was weighed. To cause the animals to lose from 10 to 20 per cent of their weights without daily fluctuations, there was considerable variation of the preoperative duration on the diet.

Open wounds were made on the dorsal surfaces of the rabbits' ears as described by Howes.[18] One square inch of skin and subcutaneous tissue was removed, leaving a central small island of skin for studying epithelization. The wounds were dressed with an ointment consisting of 1000 units of procaine penicillin per gm. of Aquaphor.

Postoperatively, the animals were given water and their respective diets *ad libitum*. The wounds were not dressed until the third day, when they were examined for color, prominence and delineation of the vessels, apparent thickness of the denuded surface and epithelization. Color photographs were taken daily.

The animals were killed at different intervals after granulations appeared. Some, however, were sacrificed earlier to correlate gross and histologic interpretations. Sections were taken of the ear wounds through the epithelial islands and at the proximal ends, where healing seemed grossly to progress most rapidly. They were prepared with hematoxylin-and-eosin and trichrome stains. Liver sections were similarly studied.

Results

These experiments affected some of the animals severely. There was a 25 per cent mortality of the rabbits fed only the low-protein diet (Group II). Animals fed the low-protein diet before and after surgery and given cortisone postoperatively had a mortality of 55 per cent from the third to the fourteenth postoperative day (Group IV). None of those that died showed visible granulations in their wounds at death. There were no deaths in the other groups.

Food intake, weight changes and gross progress of the wounds are summarized in Tables 4 and 5. Rabbits fed the low-protein diet not only received an incomplete diet but also ate less (by weight) than those fed the Rockland Chow diet. There was some starvation, therefore, of those fed the synthetic diet. In general, rabbits fed the protein-deficient diet before and afer operation continued to lose weight postoperatively with or without cortisone administration. Regardless of the preoperative diet, on the other hand, the animals gained weight shortly after operation if given a normal diet postoperatively; this trend was not affected by cortisone. A daily dose of 1.5 mg. of cortisone caused slight slowing of healing in the animals receiving the normal diet. Slight retardation of healing was noted in the open wounds in the partially depleted rabbits not receiving cortisone. However, the wounds that were most seriously delayed in healing were those of the depleted rabbits receiving cortisone and a low-protein diet postoperatively, and the granulations never attained normal thickness during the entire period of observation. Epithelization was not severely affected by any regimen.

Loss of outline of pre-existing vessels due to the appearance of an over-all velvety redness of the wound was considered to represent granulation tissues. However, in this study several consistent differences in the gross appearances of the wounds in the various groups were striking. All animals fed the normal diet postoperatively developed bright or dark reddish granulations that thickened rapidly. When cortisone was effective, however, there was a period when the tissues between the vessels were thin, smooth, white and transparent and the underlying smaller vessels remained clearly visible. As

Table 4. *Weight Changes and Wound Healing in Rabbits Fed a Normal Diet With and Without Cortisone.*

Interval from Wounding To Death	Average Daily Intake of Postoperative Diet	Weight Change after Operation	Day of Gross Appearance of Granulation	Day of Beginning Epithelization	Postoperative Weight Changes
days	*gm.*	%			
Rabbits on normal diet throughout experiment					
3	121	−5.4	3rd	None	Gradual loss
4	116	−1.7	4th	None	Lost up to 3rd day, then gained
5	91	+0.1	4th	5th	Lost up to 3rd day, then gained
4	102	−5.5	4th	None	Gradual loss
4	149	+1.5	4th	None	Lost up to 3rd day, then gained
Rabbits on normal diet throughout experiment and given cortisone* postoperatively					
12	143	+2.9	5th	7th	Lost up to 4th day, then gained
11	187	+2.5	5th	7th	Lost up to 3rd day, then gained
11	188	+1.5	6th	6th	Little change
12	154	+0.8	6th	6th	Little change

*Cortisone dosage: 1.5 mg. / kg.

the cortisone effect was lost these tissues became opalescent and eventually opaque, with a dull pinkish hue. The granulations never developed the thickness of progressively healing control wounds. The wounds of the low-protein animals without cortisone healed rapidly once granulations appeared.

Microscopical Examination

Normal rabbits not included in this series that were killed during the first three days had ear wounds that were covered with a compact layer of red blood cells on microscopical examination. Between the third and fourth days after wounding this layer either became a homogeneous film or developed the appearance of laminated fibrin. The infiltration into it of white blood cells, especially polymorphonuclear leukocytes, was variable. Collagen fibers beneath the surface covering and at the wound ends were invariably swollen during the first four days. All wounds were edematous until the fourth day, when the edema was maximal. Active fibroplasia was seen in the depths of the wound and beneath the adjacent epidermis on the third day. By the fourth day the great increase in the number of fibroblasts and in interstitial edema caused marked fragmentation of the collagen at these sites. Fibroblasts invaded the surface film by the fifth day and almost completely replaced it by the seventh day. The formation of new intercellular material was noted at the end of a week. Occasionally new capillaries were seen in the deeper layers of the wound on the third day. On the fourth day many were seen streaming toward the surface, and on the fifth day they invaded the surface film. The week-old wound in the normal rabbit was invariably composed of dense granulation tissue (Group I).

The wounds in the rabbits maintained on a low-protein diet until 15 to 20 per cent weight loss was obtained preoperatively showed the same final picture by the eighth day, although the granulations were thinner (Group II). Greater numbers of polymorphonuclear leukocytes appeared throughout the wounds than were seen in the normal animals.

Normal rabbits given 1.5 mg. per kg. of cortisone postoperatively had wounds consisting of dense granulation tissue by the eighth day. They differed from the low-protein animals by the presence of more newly formed intercellular material and fewer polymorphonuclear leukocytes.

Rabbits on low-protein rations that lost less than 20 per cent weight before operation showed healing by histologic evaluation as rapidly as did normal rabbits, provided that they were given the Rockland Chow diet postoperatively (Group III). In animals fed this diet with cortisone given after surgery, there was delay in the appearance of many of the microscopical changes usually seen (Group V). No new capillaries or fibroblasts appeared until the seventh day. The wounds were invaded early by large mononuclear leukocytes. Edema in the injured area was moderate, and the collagen fragmented without preliminary swelling. The overlying film remained thick, and the red blood cells comprising it were in a good state of preservation during the first week. This layer was relatively free of leukocytes, and epithelium was seen spreading over it after the fifth day. By the end of the

Table 5. *Weight Changes and Wound Healing in Rabbits Fed a Low-Protein Diet With and Without Cortisone.*

Preliminary Starvation Period	Days on Diet Preoperatively	Average Daily Intake of Preoperative Diet	Weight Loss When Operated on	Interval from Wounding to Death	Average Daily Intake of Postoperative Diet	Weight Change after Operation	Day of Gross Appearance of Granulation	Day of Beginning Epithelization	Postoperative Weight Changes
days		*gm.*	*%*	*days*	*gm.*	*%*			
Rabbits receiving low-protein diet throughout experiment									
7	21	69	20.9	12	71	− 0.4	5th	6th	Little change
7	32	81	16.7	16	68	−13.7	5th	5th	Greatest loss on 5th day. Some gain thereafter
7	25	103	15.2	12	50		4th	5th	
Rabbits receiving low-protein diet throughout experiment and cortisone* after wounding									
8	14	56	13.3	13	86	+ 0.4	9th	7th	Little change
7	16	75	11.9	13	85	− 8.1	7th	7th	Gradual loss
8	16	65	11.5	16	90	− 8.3	11th	7th	Slight gain to 6th day, then lost gradually
6	15	100	9.2	15	58	−18.0	14th	8th	Gradual loss
7	30	66	14.1	14	34	−24.3	10th	None	Marked loss after 7th day
Rabbits receiving low-protein diet before wounding and normal diet after wounding									
4	8	59	19.6	4	131	+12.7	3rd	4th	Rapid gain after 2 days
6	11	115	14.8	4	130	+ 7.0	4th	4th	Rapid gain after 3 days
5	10	77	14.2	6	94	+ 1.5	5th	5th	Slight gain after 4 days
Rabbits receiving low-protein diet before wounding, normal diet and cortisone* after wounding									
9	20	44	10.2	13	163	+10.4	5th	6th	Gained rapidly after 3rd day
8	21	38	15.3	16	121	+10.6	4th	6th	Gained rapidly after 5th day
7	71	67	16.6	12	112	+ 3.6	5th	6th	Gained rapidly after 5th day

*Cortisone dosage: 1.5 mg./kg.

second week the wound was composed almost entirely of compact fibroblasts that were parallel to the surface. New intercellular material was sparse and usually had hyalin-like staining properties. New blood vessels were present throughout the wound, but they were not as numerous as in control wounds. By this time epithelization was almost complete.

Wounds in the rabbits that lost from 10 to 20 per cent by weight preoperatively on the low-protein diet and were maintained on this diet as well as on cortisone after surgery showed the most profound changes (Group IV). There was no edema of the wounds until after the seventh day; then it appeared only beneath the advancing epithelium. The surface film remained thin and devoid of white blood cells until the seventh day, when a few polymorphonuclear leukocytes were noted. By the tenth day the red blood cells had lost their usual form and the layer was composed of laminated, highly refractile eosinophilic material. The collagen was swollen beneath the surface film during the first week. Fragmentation of the bundles was rare or absent. Fibroplasia did not begin until the seventh day, but by the thirteenth day fibroblasts were profuse, compact and arranged parallel to the surface. It was not until this interval had lapsed that these cells were seen invading the surface layer. A few new capillaries were seen for the first time on the seventh day. During the next three days they spread throughout the wound and were unusually dilated. They were not numerous in the surface layer until the fourteenth day. Histologically, new epithelium was manifest on the fourth day. The wounds and adjacent tissues were thin until the tenth day. Thereafter, the denuded areas remained thin, whereas those that were covered with new epithelium became thickened due to edema of the underlying tissues.

Histologic studies of the livers of animals fed the low-protein diets showed fat droplets in the parenchymal cells. The effect of cortisone on the liver was the same with regard to any of the dietary regimens. Venous engorgement was noted after six days of cortisone administration. On the tenth and eleventh days all liver cells seemed progressively to fill with glycogen. The nuclei became smaller and dense and were pushed to the periphery of the cells. This picture continued until the fourteenth day, when the cytoplasmic spaces became filled with coarse eosinophilic granules. Cells in the midzonal regions were the last to remain vacuolated. Thereafter, the parenchymal form gradually reverted to the norm.

Discussion

In the presence of weight loss caused by deprivation of protein in the diet, administration of cortisone increased the postoperative mortality and did not add to the ability of the animals in this experiment to withstand stress. Rabbits that survived the low-protein diet and wounding remained healthy. Their wounds healed at approximately the normal rate, and post-mortem examination revealed nothing grossly unusual. However, when similarly depleted animals were given small doses of cortisone postoperatively, mortality rose and 2 of the surviving animals (Table 5) became anorexic and weak. At autopsy, loss of fat depots was the only finding.

In these experiments, the usual gross criteria employed to diagnose the presence of granulations were found to be deceptive in two groups of animals. Grossly, a glistening red moist cobblestone surface with the appearance of depth and with no visible blood vessels was considered to indicate granulation tissue. When granulations were observed grossly, they were also seen histologically in the wounds of animals fed the normal diet, in the wounds of the rabbits depleted before operation and fed Rockland Chow diet postoperatively and in the wounds of those fed the low-protein diet before and after operation and treated with cortisone. However, in the wounds of the rabbits fed the normal diet before and after, or only after, wounding and also given cortisone, the gross and microscopical correlations did not exist. The microscopical elements of granulation did not appear until three or four days after this tissue was thought to be present grossly. The discrepancy was caused by the presence of a thick layer of well preserved red blood cells over these wounds. This covering had the color, configuration and depth of normal granulation tissue and did not wipe off with gentle manipulation. Moreover, it provided a good bed for growing new epithelium.

The data acquired from these experiments give us some understanding of the complicated relation among the preoperative nutritional state of the animal, the chemical evaluations of its metabolic state, the postoperative diet and the mobilization of nutrients for repairing the injury and healing the wound.

When protein was withheld from the rabbits, the total circulating serum albumin was sharply reduced at first while they lost the first 10 per cent of their weight (Fig. 1 and Table 2). Thereafter, however, this blood constituent was maintained at a relatively constant level until over 30 per cent weight was lost. Most authors have not plotted hypoalbuminemia with weight loss but have noted serum-albumin changes over prolonged periods of low-protein ingestion. Bloomfield observed an initial drop of total protein in the blood of adult rats after two to four days of protein restriction.[19] He thought that this drop was primarily in the albumin fraction. Later he showed that low-protein intake continued for a long period caused no further decline in the serum-protein concentration, although he failed to note the effect on serum albumin alone.[20] Weech and his co-workers made the same observa-

tion on dogs fed synthetic low-protein diets.[21] Torbert found that the albumin fraction fell by at least the sixth day and was then maintained at a lower level for a considerable time.[22] He observed that the blood volume was proportional to body weight but not to the protein concentration.

Investigators have shown that after injury the protein stores are mobilized in excess of the needs of the healing wound.[23-27] Most of these observations have been made on the severely injured, and the response was measured by nitrogen excretion and weight loss. In general, it has been found that restriction of food or debility before trauma has a tendency to prevent negative nitrogen balance and to diminish weight loss that occurs in normal subjects after injury. Howard and his co-workers emphasize that the catabolic process occurring after injury is not like the catabolic changes occurring after starvation or hyperthyroidism, as the latter can be altered by feeding.[24] Howard further believes that the vigor of protein catabolism depends on the intensity of the stimulus and the capacity of the organism to respond to the stimulus and that the capacity of the organism to respond is related in some degree to the previous state of protein nutrition.[25]

Regardless of the preoperative diet, all rabbits in this experiment invariably gained weight after the third postoperative day as long as they were given a well balanced diet that was eaten in sufficient amounts after operation; cortisone did not change this. In other words, their postoperative response resembled recovery from starvation depletion more than recovery from injury depletion. However, weight loss continued after operation, as expected, when the low-protein diet was again given.

Depletion of protein is known to affect wound healing. Thompson, Ravdin and Frank demonstrated markedly diminished fibroplasia at seven days in wounds of dogs that were severely depleted of protein.[28] Kobak and his co-workers[29] also observed this in the wounds of rats similarly restricted. They further noted a decreased maturation rate of fibroblasts, their failure to organize along lines of stress and the delay of reticulin maturation to collagen. Chalkley and his co-workers[30] found that the appearance of new vascular buds in the wounds of protein-depleted mice was retarded. In this experiment the amount of protein depletion alone was not profound enough to delay healing, but significant delay appeared when cortisone was also given. As with cortisone alone, the retardation was of fibroplasia and capillary growth and there was a relative absence of inflammatory elements and edema.

One of the earliest observations made by Ragan, Grokoest and Boots with ACTH was noted in sick patients whose biopsy wounds failed to heal.[4] In other words, these patients might have been suffering from protein depletion. In the laboratory, 5 to 6 mg. of cortisone per kg. was necessary to depress the appearance of granulation for twelve days, and smaller doses repressed the appearance of granulation for a shorter length of time.[3] All these animals were well nourished, received an adequate diet and did not lose weight.

The investigators who have described retardation of healing by cortisone have described somewhat different changes in explaining the nature of the inhibition, but they have agreed that inhibition occurred with both ACTH and cortisone if these were given in sufficient amounts and in the incidence of ACTH frequently enough.

Spain and his co-workers demonstrated complete suppression of all elements of wound healing in mice that were treated with cortisone. The macrophage response was significantly retarded.[5, 6] Taubenhaus and Amromin, however, thought that the administration of this drug caused the appearance of large numbers of macrophages in wounds and that collagen formation and fibroplasia were inhibited.[7] In fractures, Blunt and his co-workers again noticed the delay of granulation as well as slower resorption of hemorrhage from the fracture site.[2] Relative absence of infection and inflammation has been noted and recalls Carrel's idea that inflammation or irritation was necessary to stimulate healing processes.[31] On the other hand, diminution of inflammatory response might be an expression of an altered response to bacteria. For example, burns have been observed to heal without the usual concomitant superficial infection,[12] and although in pneumonic lungs bacteria continue to multiply, the usual inflammatory response is absent when ACTH is given.[32] Howes and his co-workers noted no difference in the bacteria counts of wounds from either control or cortisone-treated animals, although wounds of the latter animals remained reasonably free of inflammatory exudate.[3] Gross found that cortisone had a strong inhibitory effect on both acute and chronic inflammation from injections of formaldehyde.[33] Inflammatory exudate was also diminished after injection of either mineral oil or tubercle bacilli in rats treated with cortisone.[34]

The effect of hyperadrenalism on blood vessels has been emphasized. Jones and Meyer observed inhibition of capillary growth with chemical burns on the corneas of rabbits treated with cortisone.[35] Others also have noted diminished vascular congestion in the eyes of cortisone-treated persons.[36-38] Robson and Duthie found that capillary resistance was increased.[14] In our laboratory, when T-1824 dye was given intravenously to wounded and cortisone-treated rabbits, the dye diffused into their wounds less than into those of the controls. Finally, hyperadrenalism increases protein catabolism and alters carbohydrate metabolism — and, as has been said, these systemic metabolic changes alone may seriously alter the process of healing.

The clinical publications that report good healing with ACTH or cortisone are not in conflict with the laboratory investigations that reported delayed healing. Mote noted, for example, that epithelization was rapid in a burned person treated with ACTH.[11] Experimentally, the rate of epithelization is only slowed with large doses of cortisone. Crassweller and his associates observed no evidence of delayed wound healing despite cortisone therapy in high doses,[8, 9] and Whitelaw commented on adequate healing of a burn in the presence of ACTH treatment.[12, 13] Wounds healed eventually in laboratory animals if cortisone or ACTH was given other than locally, and healing always occurred after two weeks of treatment with cortisone. ACTH, unless given around the clock or in a depot, cannot continue to stimulate the adrenal gland for a sufficient length of time to mobilize the amount of steroids necessary to suppress healing. Moreover, responses to cortisone or ACTH are undoubtedly individual. This has been shown in laboratory animals, for the guinea pig forms granulation at the usual time under the influence of cortisone.

As shown here, animals partially depleted of protein that were given small doses of cortisone and a low-protein diet after wounding demonstrated considerable retardation of wound healing. It seems, therefore, that future reports on patients receiving cortisone or ACTH should indicate specifically the preoperative nutritional status as well as the postoperative intake of food and the weight change. Such information would explain some of the differences in clinical reports on healing in the presence of hyperadrenalism.

At present one can only theorize concerning the cause of the combined effect of partial protein depletion and cortisone administration. It may be additive. The direct tendency toward delayed healing caused by cortisone may be augmented by the low-protein diet. The preoperative dietary preparation may have caused some hyperadrenalism with resultant increased protein catabolism that was furthered in effect by cortisone administration. It is possible that these wounds were delayed in healing because of an uncorrected partial protein depletion as well as a direct blocking phenomenon of cortisone. Another intriguing theory is found in the work of Jailor and Seaman.[39] They noted that the rats on low-protein rations had livers that were unable to inactivate estradiol and they concluded that circulatory estrogens were increased. The livers of our rabbits could have been so affected by protein restriction that inactivation of small amounts of cortisone was impaired, with resultant higher levels of circulating cortisone.

These possibilities may be clarified by future experiments, perhaps with more precise methods than we have at present.

Summary

In rabbits it was necessary to cause more than 20 per cent weight loss by starvation and protein depletion to retard the initial appearance and growth of granulations in the healing wound.

The healing of wounds in animals partially depleted of protein and losing less than 20 per cent of weight was retarded by low doses of cortisone when a low-protein diet was given after wounding. In other words, debility and inadequate intake of protein augmented the action of cortisone on wound healing. On the contrary, healing was not retarded when a normal diet was given after operation.

This may partially explain the conflicting reports on wound healing in the presence of cortisone and ACTH administration.

The mortality was greater in wounded animals receiving cortisone after being depleted on a low-protein and starvation regimen than when cortisone was not given. Stated conversely, cortisone did not help the wounded animal to sustain stress under these circumstances.

The criterion used for the gross appearance of granulation may be deceptive. Histologically, extravasation of whole blood may under certain circumstances masquerade as granulation tissue.

The relation of total circulating serum albumin to the healing of the wound and to diet was demonstrated. The influence of starvation and low-protein diets on healing is discussed.

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URINARY COLLOIDS IN THE PREVENTION OF KIDNEY-STONE FORMATION*

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THE nature and process of kidney-stone formation has puzzled the medical profession for a long time. In the sixteenth century Paracelsus expressed the opinion that a material obtained from food constituted the basic cementing material essential to stone formation. In 1856 Meckel[1] advanced the theory that the organic gluing or cementing matrix was a product of an inflammatory condition of the urinary tract. Fourcroy and Vauquelin[2] considered the cementing substance to be albumin and gelatin. Ebstein,[3] by dissection and analysis of stones, concluded that urinary calculi contain a framework of albuminous substances. He believed that this organic material resulted from an inflammation of the urinary tract, which formed a network for impregnation by inorganic particles of the urine. Schade[4] described certain conditions necessary for stone formation. These included precipitation of crystals from a supersaturated solution containing an organic colloidal material such as fibrin and mucin, which form a nucleus of the minute calculi. Lichtwitz[5, 6] concluded that the abnormal solubility of stone-forming salts in the urine depends on the presence of certain colloids that prevent precipitation and agglutination of salts and other colloids. The latest investigations of Scherer, Claffey and Keyser,[7] on the organic components of urinary calculi, indicate that they are colloidal in nature.

Urine is a highly saturated solution of extremely complicated composition. Its basic organic constituents are urea, uric acid and its salts, formed by the oxidation of purines. In that fluid, electrolytes as well as nonelectrolytes remain dissolved in much higher concentration than their solubility in water indicates. The reason for this is that the urine of a healthy person also contains colloids that prevent the precipitation of substances in such supersaturated solutions, as long as their degree of dispersion is sufficiently pronounced. Lichtwitz was the first to determine the protective action of the urinary colloids.[5, 6]

From what is known of the effect of colloids in increasing the solubility of stone-forming salts and preventing their precipitation, it follows logically that if this protective power is diminished or is unavailable, urinary deposits will form much more readily. This reasoning probably also applies to other types of calculous formations, whether in teeth, salivary ducts, pancreas, gall bladder or prostate gland. Although during the past seventy-five years many interpretations of stone formation have suggested that a basic cause is an unbalance between colloids and crystalloids, the medical literature shows a lack of information concerning further investigations of this unbalance and a disregard of valuable information that colloid chemistry could offer. Our interpretation is that the protective action of these colloids is important in preventing precipitation, agglomeration and conglomeration of crystalloids. If the concentration of such protective colloids is insufficient, however, then the

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crystal nuclei are sensitized and stone formation is accelerated.

One of the authors, while stationed in the Pacific Area during World War II, had an opportunity to observe the incidence of stone formation among persons of many ethnic groups and nationalities. The determining factor appeared to be the presence or absence of protective urinary colloids. In 1947 the significance of urinary colloids in relation to stone formation was further investigated in West Florida, previously reported as an area of high kidney-stone incidence.[8]

Urine specimens were obtained under aseptic conditions from both male and female patients and were subjected to ultramicroscopical examination, determination of electric charge carried by the colloidal particles and determination of surface tension; the most characteristic specimens were subjected to ultra-photomicrographic studies. The ultramicroscopical studies revealed that urine from Negroes showed a pronouncedly higher colloidal activity than that from white subjects. In this connection it is interesting to report that Negroes in general are outstandingly free from stone formation. This applies to all parts of the world, including even those characterized by medical workers as "stone areas." This characteristic becomes less conspicuous when whites and Negroes have intermarried.

It could also be ascertained that the urine of females generally showed a higher concentration of colloidal matter than that of males, and that urine from pregnant women even surpassed the concentration of ultramicroscopically visible colloidal particles found in that of nonpregnant women.

Physiologic changes of the urinary tract accompanying and following pregnancy are present for from eight to twelve months. Women have an average of 2.5 children and a greater number of pregnancies. This means that physiologic dilatation and stasis of the upper urinary tract, often complicated by infection, is present for a total period of thirty months. Analysis of collected series of 49,000 obstetrical cases from various parts of the United States reveals only fifteen, or .03 per cent, complicated by stone. Also excluding the direct effect of pregnancy, women are more prone to have chronic upper-urinary-tract infection than men. From these facts it appears that if stasis and infection are the factors predominantly predisposing to stone formation, as is frequently stated, women should develop stones more readily than men. This is not true, however.

Surface-tension determinations were made with the pendant-drop method[9] from urine of various patients after it had been subjected to ultracentrifuging, whereby all matter visible in the ultramicroscope was removed. The urine of white females was found to have a pronouncedly higher surface tension than that of Negro females, the former averaging 60 dynes and the latter 52 to 55 dynes per cm. It could also be demonstrated that the surface tension of urine of both white and Negro females decreases during pregnancy. Aside from this, it was interesting to note that the amount of colloidal particles visible in the ultramicroscope pronouncedly increased with the duration of pregnancy.

Electrophoretic studies of the noncentrifuged urine samples revealed that all urines of low surface tension had been obtained from patients giving no history of stone formation, suggesting that it is the presence of capillary-active lyophilic colloids that is responsible for this favorable condition. The interpretation is advanced that the presence of capillary-active agents might be the predominant factor, due to their acting as protective colloids and dispersing agents, forming a reversible gel in combination with the crystal micelles instead of a solid crystal of inorganic matter.

It was also found that certain chemicals, — as, for example, hyaluronidase,* — are not only highly capillary-active products but will also appreciably accelerate micelle formation and will prevent stone development, because they cause the natural urine colloids to form a gel, thereby preventing the electrolytes present from crystallizing.

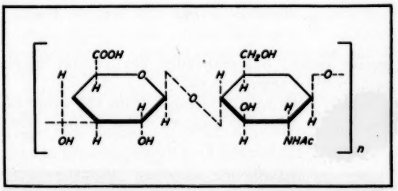

FIGURE 1. *Chemical Structure of Hyaluronic-Acid Monomer.*

Hyaluronidase is an enzyme whose molecular weight has been estimated to be between 60,000 and 70,000. Oxidizing and reducing agents destroy its activity. The same holds for reagents that attack the carbonyl group.

Hyaluronic acid, a substrate of this enzyme, is a linear or spiral polymer whose molecular weight has been estimated at from 200,000 to 2,000,000. It is composed of alternating units of acetyl glucosamine and glucuronic acid, as shown in Figure 1.[10]

Ultramicroscopical research has offered visual proof that these chemicals act as peptizing agents and protective colloids. If the urine is spread on a slide and the liquid film so formed is allowed to evaporate, and the deposit is then examined with an "Ultropak" microscope the results shown in Figures 2 and 3 may be observed.

*Supplied (as Wydase) by the Wyeth Laboratories, Philadelphia, Pennsylvania.

Figure 2 shows the deposit from the urine of a woman who had recurrently suffered from renal calculi but had now been pregnant for four and a half months. This picture is interpreted to mean that she is now forming in her urine only highly solvatized gel clusters that will readily redisperse when diluted.

Figure 3 shows the deposit obtained from the urine of a white man in normal condition. The protective colloid has embedded any crystal micelles and prevents their growth.

FIGURE 2. *Deposit in the Urine of a Pregnant Woman.*

Figure 4 shows the deposit from the urine of a white man who has suffered from kidney stones.

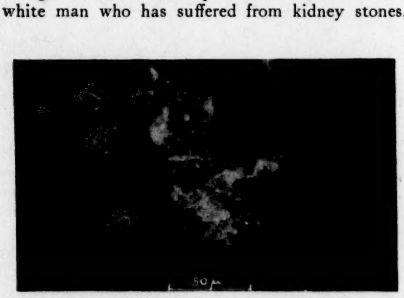

FIGURE 3. *Deposit in the Urine of a Healthy White Man.*

In addition to a few large crystals, the urine is full of solid crystal micelles that tend to aggregate and eventually grow into large stones.

Figure 5 shows the urine deposit of the same subject thirty minutes after hyaluronidase had been injected. This photograph shows that after medication the solid particles have now become the dispersed part of a jelly-like cluster.

Summary and Conclusions

Crystalloid and colloid factors relating to calculus formation in the urine are discussed and the following inference is made as to their importance:

Kidney-stone formation may be controlled by the concentration of lyophilic colloids in the urine; presumably, the higher the concentration, the less noticeable the stone formation.

Stone formation may be brought about either by the growth of crystals from a highly concentrated electrolyte solution or by the agglomeration of the dispersed phase of inorganic colloids due to a reduction of their zeta potential in the presence of a high concentration of counter ions.

In the presence of hydrophilic colloids, the electrolytes are thought to bring about gelation if present in high concentration, embedding the inorganic matter in the gel. The hydrophilic colloid, if capillary-active, may also act as a peptizing agent and protective colloid, thereby preventing growth or agglomeration.

The use of strong peptizing agents, such as hyaluronidase, may reduce stone formation.

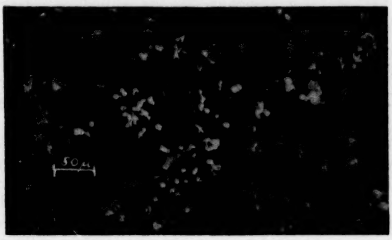

FIGURE 4. *Deposit in the Urine of a White Man Susceptible to Kidney-Stone Formation.*

FIGURE 5. *Deposit in the Urine of the Same Patient (Fig. 4) After Treatment with Hyaluronidase.*

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THE CONTRIBUTION OF PSYCHIATRY TO MEDICAL PRACTICE*

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I APPROACH my topic not from an objective point of view but subjectively, and by asking myself the following personal question: What have I learned in psychiatry that would have been useful had I known it in my five years of general practice in rural Vermont? Even here I could far more easily have spoken on the subject of what my medical practice has contributed to my knowledge of psychiatry. With this explanation I make a presentation that is predominantly anecdotal rather than the scientific document that might have been expected.

In the diagnosis of the conventional psychiatric disorders that are described in our textbooks, I do not think I made too many mistakes. There were, however, a large group of patients with disorders to which I would now attach labels quite different from those that I attached heretofore.

The woman for instance who anxiously had her blood pressure checked at frequent intervals, paced the floor in a distraught manner and was depressed and constantly worried had involutional melancholia. Today I would believe that a short series of electric-shock treatments, perhaps only six in number, would lighten her mood, relieve her agitation and make life far more comfortable for her. At the time I could see her only as an upset aging person who needed friendliness and assurance, and who with medicine for her bowels and blood pressure would be able to gain sufficient support to worry through her illness. However, this prolonged unhappiness of a year or more, with distress for both the patient and her family, could have been telescoped with a few electric-shock treatments into a few weeks, with great attendant increase in comfort to herself, her family and her neighbors.

With many of the things I now know in the area of prognosis, I believe that I would often have had a much more secure and optimistic outlook for the future when I was in general practice.

For example, the only son of a rather aloof farm family committed suicide by hanging himself in their barn. In retrospect it could be seen that he was in a emotional turmoil for two or three weeks, ever since the acquisition of gonorrhea had loaded him with shame and guilt. The mother manifested grief at that time that I incorrectly thought was appropriate. Today I would think that she was bottling up much of her emotion and was carrying on with a front of courage. About two months later she progressed from sleepless nights and poor appetite into a clear-cut case of what I then called anorexia nervosa but that I would now say was anorexia nervosa due primarily to a grief reaction over the death of her only child, to whom she had an overly close attachment. Several members of this family on both sides had been in mental institutions. This brought about a terrific fear on the part of the patient, her husband and her relatives of her being taken to the state hospital. I labored through several weeks of indecision, trying every method I could call to mind of getting her to eat and to understand her difficulty. Awareness of the family's fear of hospitalization along with my own uncertainty about the outcome led to my indecision, which did not help matters at all. Finally I called in a psychiatrist in consultation and acted on his recommendation that she be taken to the state hospital. A remarkable change came about after admission. A stalwart attendant nurse kindly but firmly insisted that she eat. Her recovery was so rapid that she was not transferred from the admission ward; some three months later she was at home, to the surprise of both the husband and myself. At the time I regarded her rapid recovery as something of a happy accident; today I believe I would expect it as a matter of course. With my present assurance of what to expect I would not have to go through the vacillating uncertainty that I had at that time, with the disturbing effect it must have had on the family and the patient.

In the wide realm of psychiatric disorders, including schizophrenia as well as manic-depressive psychosis and paranoia, we have an optimism today that, although it is becoming shared with the medical profession as a whole, has not yet fully entered the understanding of the average physician in relation to any specific patient.

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The son's death, too, suggests today a couple of points that I did not understand at the time. What seemed then to be two or three weeks of moodiness appears now to have been a frank psychosis of the nature of a schizophrenic turmoil. Fortunately for me, another physician treated him for his gonorrhea, for undoubtedly I would have made the same mistakes he did. The physician told him that there was no test of cure for his disorder — words that he took to heart and interpreted as meaning that he had an incurable affliction. It is difficult to realize sometimes how a statement of this kind may mislead a patient at the very time when he needs the greatest amount of support and understanding. Furthermore, the physician failed to recognize this patient's distress and its significance.

There was one type of patient that I tolerated poorly in practice. This was the type that I would now describe as achieving secondary gain from an illness. I refer here to the patient who appears to enjoy being sick — not only with psychiatric disorders but with medical and surgical disorders as well. Somehow it seemed wrong to me that a person should thrive on his illness, and perhaps I gave these patients as little attention as I legitimately could. In a busy practice, with priority given to some patients over others, these no doubt were far down the list. Today I believe that a person is indeed sick who is sick to a point at which illness is pleasant and preferable to the complications in which health would involve him. The older practitioner knows this, I am certain, but perhaps he came by the knowledge through years of experience rather than through the short cuts that psychiatry may furnish.

The unco-operative patient also irked me in practice. After all, what can you do for the patient who won't follow your orders, I thought. Some of this was perhaps the overevaluation that the young doctor gives to his orders. The value of things that he doubts he is forced to affirm with conviction. Perhaps some practitioners never fully outgrow the need of having obedient, co-operative patients. I am certain that I failed to understand or even to make much effort to understand why the patient would not co-operate. There were those sturdy patients who refused to "give in" to their illness, who seemingly by force of will attempted to conquer their disease. This often appeared an ostrich-like attitude of burying their heads in the sand and refusing to admit the disease that the young clinician had determined to be present. Even more embarrassing was the fact that so often these unco-operative patients recovered without subscribing to the physician's prescribed regimen. From both experience and psychiatry we can learn that certain indomitable characters refuse to submit to the doctor's authority. We even see that some of these patients are warding off an overdependent relation of which they are fearful.

I have gained something in understanding how I feel about patients. To the two large categories that I have just mentioned (the patients who achieved secondary gain from their illness and those who were unco-operative) I am certain that I did not give adequate attention. It was not because I did not try but because I was lacking in sympathy and understanding both of why the patient acted as he did and of why I felt as I did about him. Sometimes a simple realization that one is intolerant of a patient is enough to furnish a clue to the reasons for the intolerance. Understanding one's own shortcomings brings about a fairer point of view.

From psychiatry I have learned to make a prolonged attempt at understanding what the patient's problem really is, thus contributing to better diagnosis and treatment. In practice I had a fear that I was not giving the patient his money's worth of medical practice if the call had not included either some physical examination, the giving of medicine or performing a surgical operation. Although I knew intellectually that it often took hours to come to a real understanding of the patient's problems, I did not feel justified in taking the time that was necessary. Somehow this didn't seem to be the medical attention that I believed the patient expected from me and that I thought I should give; it wasn't what he was paying me for. Without this freedom to explore all the factors that could be involved in the patient's difficulty, I am certain that much of my diagnosis and treatment concerned itself only with a comparatively small sector of his distress. One of the main things that psychiatry has done is to show the physician that spending hours in listening to all ramifications of the patient's problems and life experience is a medical service just as valid as providing medicine or surgical treatment. This may be something of an illusion on the part of the psychiatrist, but if so, it is a useful one in that it gives the physician more security and confidence in coming to a broader understanding of the patient's difficulties.

One of the most outstanding pitfalls I fell into in practice was that of neglecting to weigh all the circumstances relating to the patient's illness when the first organic findings were determined. Once some sign of organic disease was found I grasped it too securely as the primary explanation of the illness. For example, I remember a very obese woman of about thirty-five who had terrific headaches. I gave much consideration to whether or not this was a true migraine and explored at some length the relation of these headaches to conflict that she was having in her relationship to her husband, which stemmed in large part from her inability to break away from her attachment to her father. Furthermore, she had distress because of her great obesity, which interfered with her usual social pursuits, thus bringing about feelings of isolation, and dissatisfaction with her own inability to control her

weight. This exploration abruptly came to an end when x-ray films of the skull showed that she had some bony protrusions of the inner table. Although the textbooks considered them usually asymptomatic,* I could only think: "Why shouldn't there be some symptoms from these bony prongs sticking down into the brain?"

I thought then that I had successfully made an important diagnosis of a rather infrequent disorder and with pleasure accepted it as an explanation of her symptoms, brushing aside all that I knew about her distress in living. It is easy to see now that however large or small an element the benign hyperostosis played, it would not detract at all from the importance to her illness of her disturbing family relations.

The whole field of psychosomatic medicine was far from foreign to me in practice. Osler said that asthma was a respiratory neurosis. In 1876 Beard had pointed out allergies as a manifestation of "American nervousness" particularly prevalent in the upper classes. In arthritis it was not difficult to see a considerable difference in the temperament of those with atrophic and those with hypertrophic arthritis. Looking back on it, I find that I gave substantial consideration to the psychic elements in one group of psychosomatic disorders — that is, asthma and the allergies, arthritis, peptic ulcer and hypertension. I was more aware of the psychic element in these disorders than in many others, possibly because of their chronic nature. The patients came repeatedly, and I came to know them better and did more extensive reading of the literature and exploration of all possible etiologic factors. Often the patients themselves would point out the importance of emotional factors that I had overlooked. In another group of disorders, those of less chronic nature, I repeatedly missed out in appraising the psychologic and social elements. These were leukorrhea, vaginitis, enuresis and hemorrhoids. The reason for my blind spot in this area was in part, at least, the presence of tangible organic disease, which deterred me from looking any further. As these disorders did not have such a tendency to chronicity and failure of response to accepted treatment, I never came to know the patients well; consequently, they never had opportunity to tell me what was really wrong with them.

In practice I had much more feeling of "respect" than now for the privacy of the individual's personal life. Not that psychiatry had given us a right to pry and probe into all the secret crannies of the individual's being, as some psychiatrists think, but at least it has placed on us the responsibility of setting the stage for giving patients adequate time, place and inclination to express to us many of their private problems.

I remember one woman who had frequent anxiety attacks, for which I gave her aromatic spirits of ammonia and supportive consolation. I knew that each anxiety attack followed marital infidelity on her part. This knowledge, however, had not been gained through any clinical insight — I had never questioned her and never gave her much opportunity for describing the stresses that may have been factors in her illness; I had learned it from the gossip of the village. This is one of many instances in which the patient's neighbors have more insight into the emotional factors than the physician himself. She was aware, no doubt, that I had heard the village gossip, but even with this mutual knowledge there never was any thought of mentioning this aspect of her life, either by her or by me. Today I am certain that somehow, somewhere, I would make it possible for her to talk about this part of her life and that through talking about it she would gain knowledge of her motivation and relief from either her anxiety or her indiscretion or both. Furthermore, I would hope that today I would more frequently make adequate investigation of the causes of the patient's anxiety so that I would not have to be alerted to it by the neighbors.

One attitude gained from psychiatry is of doubtful importance: In practice I had a greater acceptance of things as they were — that is, a less compulsive need to bring about curative change. It was easy to see the patient in the framework of his parents and grandparents, to see the morbid processes repeating themselves from one generation to another and to accept these processes as rather immutable phenomena with which there was no great need to tamper. Today I would feel a greater need to alter conditions.

I remember a man with bronchiectasis whom I furnished for five years with enormous amounts of ammonium chloride and creosote, the two remedies that he thought helped him the most. I introduced him to postural drainage and to each new preparation for bronchial liquefaction that came on the market. Over the years I became well enough acquainted in a superficial way with him and his family background to realize that he came from a family that had always suffered from "old-fashioned consumption" — the kind that is consistent with a long and useful but cough-racked life. Although I knew that there was an element of secondary gain in his disorder, — that he seemed more disabled at those times of year when farm work was heaviest or taxes were falling due rather than when respiratory infections were more prevalent, — I never thought of dealing with that aspect of his illness. Furthermore, the man was unhappy; he was depressed when he came to me. It was so easy to attribute his depression of spirits and activity to his bronchiectasis that it never occurred to me to go farther. It is almost inconceivable now that I could have failed to realize that patients with bronchiectasis are not necessarily depressed and that bronchiectasis in no wise immunizes a person against

*Benign hyperostosis of the inner table of the skull.

a depression. Although I saw this man many times over the years, I do not remember ever sitting down with him and talking at length about his troubles. Even now I have a feeling that he had some very deep fears that he would have confided in me if I had given him an opportunity. It is quite obvious now that the patient was prescribing the treatment and I was simply responding to the patient's superficial requests.

Just as I felt less inclined to tamper with the private lives of patients by investigating the influence of their hidden problems in bringing about their illness, so also did I utilize this information less in treatment.

I visited many times the family of a hired man on a farm, usually for the sickness of one or another of the children or some acute respiratory or dyspeptic disturbance of the wife. I knew even then the real genesis of the family's overfrequent illnesses, but I did nothing about it. This man was working at low wages for one of the best farmers in town. The farmer was a very driving, ascetic person who expected his help to keep pace with him. The "hired" man was the son of a moderately well-to-do merchant in a neighboring town who had grown up as a village boy with a rather sheltered childhood and with the expectation of continuing in his father's business. However, just before he was old enough to go into his father's business, financial reverses wiped it out and his father died. He was forced to take what work he could get, and although he had a poor background for farm work it furnished the money that would buy food for his children. His wife, a registered nurse, had never expected to live in the meager circumstances in which she found herself. Poorly prepared both in experience and in attitude for this life, they became more and more discouraged, with feelings of failure and inadequacy. They felt cornered, with no way out. Finally, after many years and without any professional help, this family solved its difficulties by weighing the desire for work in a store against the slightly greater remuneration from farm work and moved to a nearby small city, where the patient found work. They became quite content, with attendant diminution of ill health in the family.

It is possible that today I would still not be able to help this family with their basic dilemma. However, I can say that I saw the problem then and did nothing about it; now I would at least find hours to listen, not just to the baby's chest but to the frustrations and discouragements of husband and wife. I speak incorrectly when I say I saw the man's dilemma at that time. I saw it only in a superficial way as an uncomfortable situation for him. I see it now as an intolerable situation — one that could have caused him nothing but continuous distress and resentment.

Much of medical practice is involved with the treatment of an aging population. It is not improbable that the general physician has developed higher skills and understanding of the needs of the aged than has the psychiatrist. From psychiatry, however, I gained one idea that was of assistance to me in understanding the problems of aging persons. This idea I think I grasped in part in individual cases in practice but never carried it far enough to make it into an important generalization. It is the concept of the aging person as a rejected person. We speak often of the rejected child who was dropped from membership in the family constellation with the advent of the new baby. We speak less often of the rejected adult, yet we can see, time after time, the disorders of the aging person that follow the departure of one child after another from the family fold, thus leaving the adult more and more alone and often making it difficult for him to replace these affectional ties in any manner.

The work of Dr. Erich Lindemann on reactions of grief has alerted us to a greater perception of the late effects that are frequently caused by the ruptured ties of losing loved ones, whether through death or through departure. Often I think that I might have been able to have predicted and prevented grief reactions had I been more aware of the possible effects of each rupture of family ties.

Much that psychiatry can give to medical practice is intangible and difficult to communicate. One might say that it is a broadened view of what the physician can and should do for his patients. This breadth of perspective involves concern not only with treatment of a disease but with a substantial understanding of the patient, of his expectations and his frustrations. In practice I easily accepted unhappiness as the lot of man and not a disease and hence as no business of mine. Today I believe that the practitioner must be concerned not merely with the disease entity but with the welfare of the individual, the family and the community. This concern with their welfare must express itself not merely as a passive, benign attitude; it calls for action in the exploration of all the possible factors involved in the genesis of the person's illness and for utilization of all possible modes of treatment. It involves not only a sincere attempt to understand how the patient feels but also an attempt to understand how the physician himself feels about the patient, for no matter how well our feelings are concealed by some professional pose, they are often transmitted to the patient and also may influence the way in which we investigate and treat the patient's problem.

Some of the formulations and mechanisms of psychiatric theory serve only to distract the physician from taking the time to understand how the patient feels. They have a place in psychiatric research, but they belong there more than in the practice of medicine. The formulations can so often be used, like minor organic disease, as a means of terminating investigation by bringing about a premature sense of solution of a problem.

Much that has been said in regard to understanding the patient is not the unique property of psychiatry. With the maturing of experience the imaginative physician gains this for himself. Twenty years of seeing the problems of one's patients bring about a richness of perception and understanding that perhaps cannot be equaled by any other system of training or scientific thought. One of the basic goals of education, however, is to telescope experience so that the person has more skill throughout the active periods of his life. We would hope that through psychiatric understanding the doctor would become as perceptive of the psychologic and social needs of his patients in five years as he might from experience alone in twenty years. We note this because many men who have been in practice over a span of many years can easily and truly say: "This is old stuff. We all know this." They say it correctly, but they often forget the great length of experience that has contributed to their present understanding.

Much of the understanding that I have attributed to psychiatry no doubt came to me not from it but from my practice in northern Vermont and from the example and tutelage of my father, a Vermont country doctor. At least it is from this combined background of practice and psychiatry that these words come. When I see the young man who has gone into psychiatry directly from his hospital internship, I often think that he has missed an essential experience from which general practitioners have achieved an understanding that surpasses his. There are, no doubt, more good psychiatrists among practitioners than they imagine. The continued application of their broad human understanding, their responsiveness to the real problems of patients — that is the practice of psychiatry.

PENICILLIN SENSITIVITY OF STAPHYLOCOCCI*

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A SIGNIFICANT increase in penicillin resistance of *Staphylococcus aureus* has been reported from medical centers in this country and abroad.[1-5] In several instances the number of penicillin-resistant strains of *S. aureus* was recorded as greater than 50 per cent. This trend has been generally attributed to hospital infection from carriers of penicillin-resistant organisms and to the emergence of drug-fast strains in unhealed lesions following penicillin therapy.

Sherris and Florey have suggested that there is a close correlation between clinical manifestations of staphylococcal lesions and penicillin sensitivity of the infecting organisms.[6, 7] They found that acute, closed infections and deep-seated infections, acute or chronic, were mostly associated with penicillin-sensitive staphylococci, whereas penicillin-resistant staphylococci were principally associated with superficial wounds.

This paper reports an analysis of data relating the sensitivity of *S. aureus* to penicillin that strongly incriminates hospital infection as an important cause of increased resistance and an analysis of 155 strains of *S. aureus* that fails to confirm the findings of Sherris and Florey.

METHODS AND RESULTS

Culture sensitivity data were obtained by the filter-paper disk method. The validity of this method as a rough index of bacterial sensitivity to antibiotics has been established by comparison with the serial-dilution technic in several laboratories.[8-10] The procedure was standardized in our laboratory so that a 12-mm. zone of inhibition around a penicillin disk represented, in terms of the serial-dilution technic, inhibition of the test organism by a concentration of penicillin that is readily obtained in the plasma when customary dosages are employed. Accordingly, organisms that failed to grow around a disk in a diameter of 12 mm. or more were classified as "sensitive," and organisms that grew in a diameter of 11 mm. were classified as "resistant."

Table 1 shows trends in the incidence of penicillin sensitivity of *S. aureus* during the past five years. When *S. aureus* was cultured on more than one occasion from the same patient, only the first organism isolated was considered in the analysis. A decreasing incidence of penicillin sensitivity was first noted in 1949, but this was not sustained; 76 per cent were sensitive in 1950 as compared with 62 per cent in 1949. A marked decrease occurred in 1951, however, when only 47 per cent of *S. aureus* were sensitive to penicillin. This change was noted at the time when the nature of the surgical lesions presenting them-

TABLE 1. *Trends in Staphylococcal Sensitivity to Penicillin.*

	YEAR				
	1947	1948	1949	1950	1951
Staphylococcus aureus, number of strains	239	186	298	370	489
Sensitivity to penicillin, per cent	81	78	62	76	47

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selves for study suddenly changed. Prior to 1951 our ward population was composed of patients with a variety of common surgical infections; thereafter it was composed only of patients with extensive, deep burns.

Correlation of culture sensitivity and types of lesions was attempted in an analysis of 155 consecutive individual strains of *S. aureus* isolated from as many surgical lesions at a time when decreased penicillin sensitivity had not yet been observed (Table 2). The patients with gunshot wounds were Korean casualties who were first seen about thirty days after injury and who had received one or more courses of penicillin before admission. These wounds were deep penetrating or perforating and, in all instances, suppurating. One patient had a popliteal abscess due to a penicillin-resistant staphylococcus, with bacteremia apparently caused by the same organism. It was also resistant to streptomycin, aureomycin, chloramphenicol and terramycin, but was moderately sensitive to neomycin. The other lesions listed are typical of those seen on a large surgical service in a general hospital and warrant no special comment.

TABLE 2. *Relation Between Sensitivity of* S. Aureus *to Penicillin and Type of Lesions.*

TYPE OF WOUND	NUMBER OF STRAINS		
	PENICILLIN SENSITIVE	PENICILLIN RESISTANT	PER CENT RESISTANT
Gunshot wounds	35	8	18.6
Burns, thermal, granulating, less than 10 per cent of body surface	22	10	31.2
Abscesses, furuncles, and carbuncles	16	4*	20.0
Chronic osteomyelitis with acute flare-up	14	12	46.1
Infected superficial lacerations	11	3	21.4
Ulcers, circulatory	6	1	14.2
Peritoneum	3	1	25.0
Soft-tissue sinus tracts	2	2	50.0
Pressure sores	0	2	100.0
Wound infection (postoperative)	0	3	100.0
Totals	109	46	29.6

*One patient had associated bacteremia.

It will be noted that the nature of the lesion does not permit categorization with regard to staphylococcal sensitivity or resistance to penicillin.

DISCUSSION

Before 1951, when we were treating wounds of relatively small extent, cross infection could be effectively prevented by rigid aseptic technic. After that time only extensive infected burns were treated; in these, cross infection was repeatedly proved to be abundant on our service despite strenuous efforts to combat it. The dramatic decrease in penicillin-sensitive strains of *S. aureus* and uncontrolled cross infection occurred simultaneously. Summers recorded 24 per cent resistant strains in outpatients and 50 per cent in hospital patients.[5] These figures are in close agreement with our finding of 24 per cent resistant strains without cross infection and 53 per cent with cross infection. Unfortunately, the role played by previous penicillin therapy cannot be entirely ruled out, since the burned patients had in general received larger doses of penicillin for a longer period of time than had those with other wounds.

If the results of Sherris and Florey could be substantiated in several centers, the need for antibiotic-sensitivity testing in staphylococcal infections would be considerably lessened. One could then give penicillin in acute closed and deep infections with considerable assurance that the proper antibiotic had been selected. Such an assurance is not furnished by our data. The nature of the lesion in this analysis did not significantly parallel staphylococcal sensitivity to penicillin. Culture-sensitivity testing remains the only true criterion of drug selection.

SUMMARY

Evidence is presented indicating that cross infection may largely explain the increased resistance of *S. aureus* to penicillin. An analysis of 155 wounds revealed that the sensitivity or resistance of staphylococci cannot be predicted from clinical observation.

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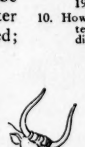

MEDICAL PROGRESS

PROGRESS IN OBSTETRICS

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THE general improvement in maternal morbidity and mortality rates during the past years is due to many factors. Prenatal care is one of the most important. In a hospital clinic that accepts all emergencies it is very impressive that a large proportion of obstetrical problems occur in the patients who have had inadequate or no prenatal care. Such cases of eclampsia as are seen today are largely from that group. Many cases of severe premature separations of the placenta occur in patients who have developed an unobserved pre-eclamptic toxemia. Cases of dystocia are more common in the patient in poor physical condition. Post-partum hemorrhage appears to be more frequent in this group.

Most important in prenatal care is proper diet. The primary factor in diet is a definite sodium restriction. Proper regulation of weight is dependent on this. The very great majority of women who gain over 20 pounds during the period of gestation are retaining fluid and are not putting on fat. This is shown by the rapid loss of this weight following delivery. Many women show edema of the legs during pregnancy. Fluid retention of serious import is largely hidden edema shown by rapid and excessive gain in weight. Any patient who gains 5 pounds in a week is retaining fluid. It is from this group that pre-eclamptic toxemia arises. Once pre-eclamptic toxemia has appeared, clinically, it is an irreversible disease until the pregnancy is terminated. If these patients can be prevented from retaining fluid, a large portion of pre-eclamptic toxemia will be eliminated. Fluid retention can be prevented in most cases by a low-sodium diet. Low-sodium intake is difficult to attain. With the marked preponderance of canned food in the average diet, a great deal of salt is ingested. Various antacids contain much sodium. What the average woman considers a low-salt diet is too high for pregnancy. Careful instruction and printed diet lists are most important in controlling this problem. The ideal treatment of any pregnant woman who shows a rapid and excessive weight gain is hospitalization. This may be economically difficult and may be resisted by the patient, but this is the only sure and safe way to eliminate the retained sodium and fluid. The fact that many women retain excessive fluid and do not have complications is no reason to be casual about this problem.

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Another important factor in prenatal diet is a high-protein diet. The fetus needs a large amount of protein for growth and will take this where it can. If the mother does not have a high protein intake, the fetus will still take protein from the mother. This may cause a lowering of the blood proteins, anemia and other ill effects on the mother.

Fat is poor food for the pregnant woman and has a high caloric content. It is poorly metabolized and digested.

A well regulated diet consists of a high protein intake, green vegetables, fruits and salads, low fat and low sodium. Carbohydrates and starches are of little significance unless combined with fat. Iron should be taken daily, as, in addition to hemodilution, the pregnant woman tends to develop anemia.

Management of threatened and repeated abortions is a common problem. Abortion is primarily due to the fact that Nature will discard imperfect products of conception. Examination of tissue passed in abortion will show as high as ninety per cent of disease and maldevelopment. Hertig and Rock[1] have shown in a series of 28 early human conceptuses, from the uteri of 136 fertile women, that of 12 early pregnancies interpreted as abnormal 7 would certainly abort. None of these showed any clinical or pathological evidence that maternal environment in itself played any part in the production of the abnormal ovum. Apparently the defective fertilized ovum is due to intrinsic "germ plasm" quality, and this is the main factor in the production of spontaneous abortion. In this series none of the patients had missed an expected period; hence the specimens were younger than sixteen days.

From these findings and much other evidence, it can be assumed that in about 90 per cent of patients who do abort the pregnancy has become worthless by the time that symptoms of abortion appear. It is true that some patients bleed early in pregnancy and then go on to produce a normal full-term baby. The bleeding in these cases is evidently not due to any defect of the ovum. Clinically it is impossible to differentiate the two types of bleeding unless the patient develops uterine cramps. In the patient who bleeds without threatening to abort, a few days' rest will usually clear up the symptoms.

Colvin and his associates[2] have stated that there is no satisfactory way of determining the life or death of the fetus. In 1570 cases of bleeding, 28 per cent aborted and the rest went to term. In 4

per cent of the abortions the cause could not be determined and theoretically might have been benefited by hormone therapy.

It may be assumed that when a patient bleeds early in pregnancy, if the bleeding is due to disease or damage to the ovum, the abortion is desirable. If the bleeding is extraovular, the pregnancy will probably proceed to a successful termination. Once the bleeding has occurred, hormone therapy gives no better results than in those in which no hormones were given. Hormones may delay the actual occurrence of abortion but will not prevent it.

The present treatment of threatened abortion consists of rest in bed for a few days without hormone therapy. After this, the patient is allowed limited activity. If pain and cramps develop, no medication is given and the patient is allowed to abort spontaneously. Should the patient bleed excessively or begin to pass pieces of tissue, a dilatation and curettage should be done.

After an abortion the patient should be carefully checked to rule out any pelvic disease. A basal-metabolism test is important. If the test is not on the positive side, the patient should be started on thyroid therapy before undertaking another pregnancy. Poor thyroid function is one of the common causes of abortion and the one that is most easily corrected by proper therapy. The author believes that any patient who has had an abortion should be put on thyroid therapy prior to conception, as the damage may well occur at the time of conception. The husband should also be examined for health and fertility.

The problem of therapeutic abortion is one that from a purely medical point of view is becoming much more infrequent. The tendency in recent years has been to treat the disease and leave the pregnancy alone. Many conditions such as tuberculosis and heart disease, which used to be considered indications for therapeutic abortion, are no longer believed to be such. Active tuberculosis can be treated during pregnancy, with no danger to the child, if the proper precautions are taken.

Tietze[3] has summarized 3592 therapeutic abortions reported in the city of New York in the period of 1943–1947. There was a proportion of 8 in private patients to 1 in service patients. This in itself is a significant figure. The most frequent indications listed were heart disease, nonmalignant tumors of the uterus, mental disorders, toxemias of pregnancy, tuberculosis, hyperemesis gravidarum and rubella.

Nonmalignant tumors of the uterus, presumably fibroids, are no indication for abortion. The majority of women pass successfully through pregnancy with fibroids of varying size. Mental disorder is reported as an increasing indication for therapeutic abortion. It is dismaying to the obstetrician to note the frequency with which therapeutic abortion is recommended by the psychiatrist. In many cases the psychiatrist is merely hopeful that the patient's condition will be improved without having any actual knowledge that it will be. It is possible that in many cases it will have the opposite effect. In only the rare case do the psychiatrists claim that the mental state of the mother will have any effect on the unborn child. As for hereditary mental deficiency, that is more a sociologic and legal problem than a burden to be assumed by the physician. There is definite danger in the assumption that the patient who has rubella in the early weeks of gestation should have the pregnancy terminated. The diagnosis of rubella is sufficiently vague to be easily abused. In addition, many healthy children are born from mothers who have had rubella. Other virus diseases may affect the infant, but we cannot assume that these are indications for abortion. Hyperemesis is a disappearing disease; with proper treatment it should never be an indication for abortion. It is the impression of the author that most of the original recommendations for therapeutic abortion come from physicians other than obstetricians. It is thought that the profession, as a whole, should have a better understanding of the problem.

Pelvic tumors appearing during pregnancy are a problem to the obstetrician. The individual case must be judged on its own merits, but certain general rules are of value. If possible, it is of importance to differentiate tumors attached to the uterus and those arising in the ovary. Uterine tumors usually consist of uterine fibroids. Uterine fibroids grow rapidly during pregnancy and tend to involute after delivery. It is hard to judge during pregnancy what the nonpregnant size of the tumor will be. Fibroids are of two general types — those that are symptomless and those that cause acute symptoms. In the type without symptoms, regardless of size, they are of importance as capable of obstructing the birth canal. If they do not obstruct the birth canal, they rarely interfere with a normal labor and as a rule do not cause post-partum complications. If they are in a position to interfere with the engagement or descent of the head, they are an indication for cesarean section. It is inadvisable to remove fibroids during pregnancy because of the danger of interrupting the pregnancy and the difficulty of hemostasis. Should they be of sufficient significance to indicate surgery, myomectomy should be performed some months after the termination of the pregnancy.

In the type of fibroid that shows acute symptoms during pregnancy, it is advisable to treat the patient symptomatically and avoid surgery. Many of this group are fibroids in the lower-uterine segment that cause pain and pressure symptoms early in pregnancy. As the uterus grows sufficiently to pull the fibroid out of the pelvis, the acute symptoms tend to subside. Those on the upper part of the uterus that cause pain and tenderness can be treated

by pain-relieving drugs, and the acute symptoms will subside. It may take days and sometimes weeks for the patient to obtain complete relief. In spite of this, there is no real danger to the patient, and surgery is rarely indicated.

In those patients who have had a myomectomy in the nonpregnant state, it is important to know how extensive a myomectomy has been performed. If the uterine cavity has not been opened, there is little danger of uterine rupture during pregnancy. If the fibroid has involved the uterine cavity and the cavity is widely exposed, cesarean section must be considered. As a rule, the uterus heals well and strongly after such a procedure.

It is not unusual to find a cystic ovary early in pregnancy. Many of these will disappear with watchful waiting. Surgery should not be performed before the fourth month, by which time the placenta has fully assumed the function of the corpus luteum. If, at this time, there is an ovarian cyst larger than an orange or any solid ovarian tumor, it should be removed. One must be careful not to be misled by a large corpus luteum. Any ovarian cyst that causes acute symptoms during pregnancy must be removed immediately.

Bleeding in the third trimester of pregnancy continues to be an obstetrical hazard. The treatment of each case must be individualized. Aside from lesions of the cervix, abnormal bleeding in the third trimester is due to placenta previa, premature separation of the placenta or rupture of a marginal sinus. At times the differential diagnosis is easy; at others it is difficult. In certain cases of severe and profuse hemorrhage it is advisable to perform a cesarean section immediately, without making a differential diagnosis. This is the quickest and most efficient method of stopping the hemorrhage. In the majority of cases the hemorrhage is less severe, and a differential diagnosis is important in determining the treatment.

The painless bleeding of placenta previa, with no uterine irritability or tenderness, is quite characteristic. If, in addition, there is a history of previous episodes of staining in the same pregnancy, the diagnosis becomes probable. In bleeding of the last trimester of pregnancy, the first and most important step is to hospitalize the patient. No such patient should be kept at home, even under the most careful observation, as an uncontrollable and fatal hemorrhage may occur at any moment. Once the patient has been admitted to the hospital she is relatively safe, as emergency treatment may be given in case of further bleeding.

There is a growing tendency, in recent years, to treat placenta previa conservatively. In those cases that have had a moderate amount of painless bleeding before the fetus has become viable, watchful waiting in the hospital may mean the difference between a living and a dead baby. Such patients must be confined to bed; their blood must be typed and matched, and donor blood must be kept ready. Should a fresh hemorrhage occur, immediate treatment must be instituted. However, many of these cases will progress safely for two to three weeks or until the baby has reached sufficient maturity. Patients treated in this manner should have no vaginal or rectal examinations until termination of the pregnancy is deemed desirable. Even a rectal examination may start a fresh hemorrhage, which may force the obstetrician's hand.

Should a patient bleed sufficiently to require immediate delivery, or should the baby be sufficiently mature, the type of treatment must be decided on. To confirm the diagnosis and affirm the degree of previa, a sterile vaginal examination is indicated. This must always be performed in an operating room in readiness for a cesarean section. No matter how carefully the examination is done, it will occasionally initiate hemorrhage, necessitating section. If one finds a complete placenta previa on examination, section should be performed immediately. This is the accepted treatment for this condition. No attempted insertion of a bag or rupture of the membranes should ever be tried. If a partial or marginal previa is present, the condition of the cervix is the important factor in determination of the type of treatment. With a multiparous cervix that is soft and partly dilated, in which there is room to effect the procedure without disturbing the placenta, rupture of the membranes is the procedure of choice. It is preferable that the presenting part be engaged. With a long, firm and undilated primiparous cervix, the safest procedure is cesarean section. Rupture of the membranes with an unfavorable cervix will result in a prolonged and ineffectual labor, with the possibility of dangerous blood loss during this period. The author does not recommend the use of a bag in any case of placenta previa. Rupture of the membranes results in an equally good tamponade of the placenta. Labor will progress to its normal conclusion; on the other hand, the bag usually comes out before the patient is fully dilated. There is more danger of infection and prolapse of the cord with the use of the bag. Finally, the insertion of the bag is more traumatic and more likely to cause hemorrhage than is rupture of the membranes.

The treatment of premature separation of the placenta causes more controversy than that of placenta previa. There are three important factors in premature separation of the placenta on which the treatment of the case must be decided. These are the amount of hemorrhage, the size and condition of the baby and the general health of the patient. If there is a mature and living child, cesarean section offers the best chance for the baby. One can never tell at what point sufficient separation of the placenta will take place to kill the fetus. If the hemorrhage is profuse and continuing, cesarean section offers the safest and most efficient way of

controlling the bleeding. Even in the case of a dead baby, cesarean section may be the best method of stopping the hemorrhage. Should the baby be dead and the hemorrhage not profuse, delivery from below is the usual procedure of choice. Many of these patients will start in labor as the result of irritation from hemorrhage into the uterus. In others, if the cervix is favorable the membranes may be ruptured. Blood replacement is extremely important, and the patient must be in reasonably good condition before any treatment is attempted. The use of the abdominal binder and the vaginal pack has largely been discarded.

The work of Weiner, Reid and Roby[4] suggests a real danger in delaying delivery in severe cases of premature separation of the placenta. A defect in the blood-coagulation mechanism may develop. The blood changes are characterized by a decrease in fibrinogen concentration and prothrombin activity and by the presence of a circulating fibrinolysin. The detection of these blood changes requires repeated observations of the size and stability of the clot formed by the patient's venous blood when incubated at 37°C. The longer the period between the original separation and the delivery of the child, the more likely is this condition to occur. The treatment is replacement therapy with fibrinogen and whole blood. Most patients will respond to this treatment, and the blood will begin to clot. However, an occasional case will come to hysterectomy as the only procedure that will stop the hemorrhage.

Bysshe,[5] in a report of 340 cases of premature separation of the placenta, states that approximately half of the series were offered no specific treatment, as premature separation was merely suspected during labor and not diagnosed until after delivery. These patients had few clinical symptoms. In the more severe type in which the diagnosis was made previous to labor, 44 were treated by cesarean section and the others were delivered from below. In 24 per cent of the whole group, pre-eclamptic toxemia was present. In many cases cesarean section was indicated with a dead baby, to check bleeding and prevent further shock.

Hysterectomy for a Couvelaire uterus is still performed. The general tendency is to remove fewer uteri. With proper blood replacement and supportive treatment, many severely injured uteri appear to function well and return to their normal state.

The third cause of bleeding in the third trimester is rupture of the marginal sinus. The clinical diagnosis is largely dependent on the ruling out of the other causes of bleeding, premature separation and placenta previa. These patients with rupture of the marginal sinus usually do not bleed sufficiently to cause alarm, but they may bleed steadily throughout labor, suggesting a marginal placenta previa. The condition is most often present in the circumvallate type of placenta. A careful examination of the placenta will show a fresh, adherent blood clot attached to the marginal sinus, and underneath the blood clot a perforation of the sinus the size of a pencil or larger. It has not been the author's experience that this condition is sufficiently acute to interfere with the normal course of labor.

Pelvimetry is an important part of the care of the pregnant woman, but any honest obstetrician will admit that the final solution lies in the labor itself rather than in previous measurements. Many excellent obstetricians have given up external pelvimetry, and many others place little faith in these measurements. The only external measurement of value is the measurement of the outlet, as so many variable factors are present.

X-ray pelvimetry has had increasing publicity and use during the past years. Unquestionably this method is of value, but it certainly is not the final answer. Primiparas with unengaged heads should be given x-ray examination; this is also true of abnormal presentations. Routine x-ray pelvimetry is unnecessary and not indicated. If there is an abnormal presentation or a question of disproportion, x-ray measurements are of help. It is a rare case in which pelvimetry gives a definite answer. It is a mistake for the obstetrician to shift his responsibility for decision to the roentgenologist. The x-ray film gives no accurate idea of the size of the fetal head or of the efficiency of labor, both of which are usually as important as the size of the pelvis. The only real answer to a question of cephalopelvic disproportion is a test of labor. Moreover, the test of labor is an excellent test of the obstetrician. A true test of labor must be judged from the time that the cervix starts to dilate until the patient has had several hours of efficient labor. Too often we are deceived by false labor or inefficient uterine contractions. If the cervix is dilating and the uterine contractions are strong and efficient, we can judge true lack of progress. Allowance must be made for vertex posterior and other abnormal presentations.

Patients with prolonged labor fall into three main groups: cephalopelvic disproportion, abnormal presentation and uterine inertia. There may be a combination of these. Occasionally an obstructing tumor may be present, but this is usually recognized in advance. Any case in which definite cephalopelvic disproportion is present should be treated by cesarean section.

The most common malposition is occiput posterior. Often labor is not prolonged, and frequently the position is not recognized until the time of birth. In other cases, a long and protracted labor strongly suggests this complication. In delayed labor in which the uterine contractions are efficient but there is lack of progress, a sterile vaginal examination may be indicated to determine the position. Beard[6] describes two types of occiput posterior —

one in which the occiput is at or behind the sacroiliac joint and another in which the occiput is anterior to this joint. In the first, or what he calls the true occiput posterior, he advises a manual rotation and allowing the patients to deliver. In the second, he believes that they will deliver without interference. Generally speaking, the treatment is to help these patients to progress normally through labor to full dilatation. Labor is then allowed to continue, in the attempt to rotate the head. Depending on the patience of the obstetrician, a variable and large majority of these will rotate naturally. A small percentage will rotate posteriorly into the sacrum. These usually must be turned by the obstetrician. Manual rotation followed by the application of forceps is the procedure of choice. Where this is not possible a Scanzoni maneuver may be performed or the Kielland forceps used. Occasionally it is extremely difficult to turn such a head without severe trauma to the birth canal and the baby. There is a growing tendency to deliver this type in the posterior position, following a wide lateral episiotomy. There is no specific length of time during which the second stage should be allowed to continue without interference. If there is no fetal distress and the mother is in good condition, three to four hours is not too long.

Cox[7] recommends that breech positions be allowed to progress until the patient expels the baby's anus; the aftercoming head is then delivered with forceps. This is sound advice, as it is difficult to estimate full dilatation with a breech presentation. If one attempts to deliver before this, the cervix may not be fully dilated. Cox also states that the mortality in breech presentations rises markedly if the weight is over 7½ pounds. A breech presentation with an ample pelvis is no indication for cesarean section. A large baby, particularly in elderly primiparas, may be an indication for section. In questionable cases a test of labor should be tried before any radical measures are taken. Young women with good pelves should, and usually do, deliver breeches without difficulty or complications. Stevenson[8] recommends that breech presentations be turned by external version if they persist after thirty-two to thirty-four weeks of pregnancy; he states that unfavorable results are rare. The fetal heart is carefully observed, and if there is any embarrassment after version the fetus is returned to the original position. This procedure is well accepted and frequently performed in many clinics. However, many external versions return to the breech position later in pregnancy. Furthermore, many breeches turn of their own accord during the latter part of pregnancy. The solution of this problem lies in determining the causes and reducing the incidence of breech delivery.

Uterine inertia is a trying and not uncommon problem. This is predominantly a complication of primiparas. Willson and Alesbury[9] state that out of 118 patients 101 were primiparas. The primary handicap is irregular and poor uterine contractions. These authors did not believe that artificial rupture of the membranes was of any material help. Eleven of their patients received oxytoxic drugs during labor; only 3 were benefited. Eight were delivered by cesarean section. In 13 the cervix was incised; in 11 it was manually dilated. These authors recommend heavy sedation for rest and sleep, six to eight hours out of twenty-four, 2000 cc. of fluids, penicillin, x-ray examination and rupture of the membranes when progress stops.

Daro and Gollin[10] ruptured the membranes in all their cases and in 32 per cent this treatment was adequate. They state that posterior-pituitary extract was effective in 95 per cent of the patients who failed to respond to rupture of the membranes.

The advent of pitocin given intravenously in very dilute solution has, in the author's opinion, proved a satisfactory answer to the problem of uterine inertia. Several warnings must be given concerning the use of this method. One must be sure that there is no cephalopelvic disproportion. Abnormal positions must be ruled out. Once one is sure that uterine inertia is the cause of delayed labor, intravenous pitocin may be given. It is recommended that not more than 5 minims to 1000 cc. of fluid be used. The flow should be limited to 30 drops per minute. It is essential that the obstetrician observe the patient personally. As soon as the contractions become regular and strong, the intravenous drip is stopped. It is always possible that if the stimulation is too strong and given too long a rupture of the uterus may result. The occasional tetanic contraction resulting from the use of intramuscularly given pitocin, even in small doses, is rarely seen following the use of such a dilute preparation intravenously. Rupture of the membranes increases the efficacy of the intravenous pitocin and decreases the amount needed. The intravenous use of pitocin is not recommended in occiput posterior.

Artificial induction of labor is an important obstetrical procedure. The indications vary greatly, and there are few absolute indications. Miles[11] reports 300 inductions. He concludes that it is a safe procedure, with a tendency to shorten labor slightly. Three procedures are mentioned: medical induction with pituitrin; rupture of the membranes; and the combination of the two.

To try to induce labor with an unfavorable cervix is unwise and frequently unsuccessful. If the cervix is not ready, labor either may not result from attempted induction or may be long and difficult. A favorable cervix is one in which the cervix is soft, taken up and partly dilated. Primiparas are usually unfavorable patients for induction. The cervix should be at least a finger dilated before induction is attempted. In multiparas the cervix should be patulous to two fingers. In addition, it is desirable that delivery be a vertex presentation with the

head engaged. This maneuver should never be attempted on a breech presentation or on a high or unengaged head. If the vertex is well down in the pelvis, there is little or no danger of prolapse of the cord. It takes considerable experience with rectal examinations to be able to judge the cervix correctly. In some cases a sterile vaginal examination is desirable for certainty.

For a medical induction, intravenous administration of a dilute solution of pitocin is the most effective method. This will succeed only if the patient is about ready to go into labor. Even with a favorable cervix on examination, many patients fail to respond to this stimulation. They will develop regular uterine contractions that will continue as long as the solution is being given, but there will be no change in the cervix. As soon as the pitocin is stopped, the contractions will cease. Those that respond successfully will continue in good labor, and the cervix will dilate during and after the use of pitocin. This is an uncertain method and it is extremely difficult to predict which patients will respond to stimulation.

If the cervix is physiologically favorable, rupture of the membranes will start a patient in labor. There is a varying interval between rupture and the onset of labor. One patient may start immediately and the next may delay several hours to a day. One must be sure that both layers of the sac are penetrated. It is possible to rupture the outer layer and obtain a small amount of fluid without actually rupturing the sac. A long Allis clamp is an excellent instrument for grasping the membranes.

The combined method of rupture of the membranes followed by intravenous administration of pitocin is the most successful and efficient. The patient starts readily in labor and has excellent contractions and an efficient labor. Again, it must be emphasized that once the patient has started in active labor the pitocin must be stopped.

A frequent question is whether postmaturity of the fetus is an indication for artificial induction. In general the answer is no. There is not sufficient certainty in the dates of most patients. There is a variation in the length of gestation. An occasional patient who is overdue by dates may have a decrease in the size of the uterus. An old-appearing infant may be born — that is, small and dehydrated. Some of these do not survive. The large majority of patients who are overdue have a normal labor and delivery. Induction will sometimes result in the birth of a premature baby as a result of mistakes in dates. Moreover, some patients who are overdue by dates have a tendency to uterine inertia. A difficult labor may follow induction in such cases.

In conclusion, one might ask: What are the indications of artificial induction of labor? The answer to this question must be left to the individual physician. Certain marginal placenta previas and premature separations of the placenta are treated in this fashion. Other complications may make the termination of labor desirable when the cervix is favorable. Multiparas who live far from the hospital and in whom the head is on the perineum and the cervix dilated may be safely induced.

During the past twenty years there has been a general increase in reliance on cesarean section. Dieckmann[12] reports a constant incidence during the past eighteen years of 5 per cent. Most other clinics report a rise. Kistner[13] reports a doubling of incidence, with a present rate of 1 per cent. Cody[14] states that in his clinic the incidence has risen from 0.5 per cent to 1.5 per cent during the past ten years. These two reports show a lower incidence than in most clinics. Lawrence[15] reports a present incidence of 3½ per cent, a fivefold increase since 1926. To compare data of the different clinics would involve a careful study of fetal damage and loss and of maternal damage necessitating surgery in later years. An incidence of 4 to 6 per cent of cesarean sections seems to be a fair average.

Indications for cesarean section have not changed. Cephalopelvic disproportion, following a test of labor, is one. Certain types of placenta previa and premature separation of the placenta, acute preeclampsia, transverse lies and large breech presentations in elderly primiparas are usually treated by section. There are many less common problems in which cesarean section may be indicated.

The type of cesarean section most commonly used is the low-flap type, with either transverse or vertical incision of the uterus. The classical section still has a place in placenta previa and in other cases in which speed is of primary importance. The extraperitoneal section appears to be losing its popularity. In the potentially infected case, a low-flap operation with antibiotics appears to be a safe procedure. The use of the antibiotics during prolonged labor with ruptured membranes is an additional safety factor. The extraperitoneal section is a more difficult operation, involving potential damage to the bladder. The extraperitoneal section has been used in conjunction with the antibiotics; Dantuono[16] reports 70 low-flap cesarean sections following prolonged labor with no maternal mortality and no excessive morbidity. Dieckmann[12] recommends cesarean hysterectomy for frankly infected cases. This is the operation of choice in many clinics. A frankly infected patient has a low fertility rate in later years, and further surgery for complications is not uncommon when the uterus is left in place.

The third stage of labor remains one of the most dangerous periods of pregnancy. There are still many maternal deaths as the result of hemorrhage. Although many cases of hemorrhage are unavoidable, others are due to improper conduct of labor and traumatic delivery. A tired patient who has had a long and difficult labor is more prone to hemorrhage. A traumatic delivery, with lacerations

and considerable blood loss, tends to cause an atonic uterus. Overdistention of the uterus from twins, hydramnios and other causes may result in uterine atony. Internal podalic version is a potential cause of rupture of the uterus. Any patient delivered from below who has had a previous cesarean section is a potential candidate for rupture of the uterus.

Retention of the placenta after delivery is not unusual. This may frequently be combined with atony of the uterus. A retained placenta may bleed excessively or moderately. Over a long period, even minor bleeding may add up to a considerable amount. Manual removal of the placenta has become an accepted obstetrical procedure. Depending on the amount of bleeding, one may wait varying periods of time for a placenta to separate. The patient must be carefully watched and all blood loss checked. If the placenta does not separate within an hour, manual removal may be done. Many obstetricians do not wait this long. In removing the placenta, one must be careful that it is not firmly adherent. If the placenta does not separate easily it is better to stop and think than to pull it off in pieces. Although a true placenta accreta is rare, adherent placenta can cause much hemorrhage without being a true accreta. In the usual case the placenta is separated with ease.

Uterine atony is a dangerous complication. The loss of blood may be rapid. Pitocin (intramuscularly) and ergotrate (intravenously) should be used freely. Massage of the uterus is of help. No obstetrician should break his asepsis after delivery until the uterus is functioning properly. Much loss of blood may be avoided if the lower uterine segment is grasped with a hand in the vagina and the fundus grasped through the abdominal wall, the uterus being compressed between hands. Acute hemorrhage may be largely stopped. With patient continuation of this maneuver, the uterus will begin to contract. Packing the uterus at this point has many disadvantages. The pack prohibits the uterus from contracting down to its post-partum size; it conceals hemorrhage; it may be a source of infection and when removed may start a fresh hemorrhage. In addition, it gives the obstetrician a false sense of security and he may prematurely leave the patient unattended.

No matter what method one uses, a few patients will require hysterectomy to stop hemorrhage. Waiting too long is dangerous if the hemorrhage is not controllable.

Blood replacement in third-stage bleeding is a vital part of treatment. When a patient shows signs of uterine atony and hemorrhage, blood should be obtained quickly. It is poor obstetrical practice to allow a patient to show definite signs of blood loss before blood is given. The appearance of shock not only means excessive hemorrhage but prevents proper function of the uterus.

In rupture of the uterus, hemorrhage may be largely concealed with little external bleeding. Any patient with a previous uterine scar or any patient in whom the type of delivery would offer any possibility of a rupture should be given a uterine exploration after the delivery of the placenta.

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MEDICAL INTELLIGENCE

PHYSICIANS IN ART

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BOSTON

THE physician has within him the qualities of the artist — the nature that led him into the study of medicine and his training in observation and appreciation of the human being. In his art, the physician derives complete relaxation from tension and from the cares of medicine. He learns to "work by the side of work." It is a hobby that gives lasting renewal of energy and spirit. The results of his energies expended in his art go out to the many who appreciate the beauties of nature and help them to forget the drudgeries of daily life. And, last but not least, with paint or clay, the physician, after retirement from his days of busy practice, has an interest that keeps him young and happy.

The late Frederick J. Cotton, physician, surgeon and artist of note, saw the value of this hobby when he showed his sculpture in the New York Physicians' Art Exhibit prior to the first exhibit held by the physicians of Boston interested in art, at the Boston Medical Library, from November 30 to December 14, 1927. A committee of nine men, among whom were the late Dr. George H. Monks and Dr. Cotton, made the arrangements for this exhibit under the expert guidance of Mr. James F. Ballard, director of the Library. The 60 exhibitors, numbering among them some of Boston's leading physicians, demonstrated exceptional ability in all the media, Dr. Cotton alone contributing 11 sculptures, 1 oil painting, 3 watercolors and 6 pen-and-ink drawings.

Inspired by the success of this first exhibit, Mr. Ballard, who was instrumental in making it such a success, at the suggestion of Dr. Cotton and myself notified the exhibitors of a meeting to organize a physicians' art society in Boston along the lines of the New York Society. As a result, a committee consisting of Drs. Cotton, Wiggin and Barney met at the Boston Medical Library on April 28, 1933, and the "Physicians' Art Society of Boston" was founded, with Dr. F. Dellinger Barney as president, Dr. Frederick J. Cotton as vice-president and Mr. James F. Ballard as secretary-treasurer. The first executive committee consisted of Drs. Lewis W. Hill, Eli C. Romberg, Somers S. Sturgis, Grantley W. Taylor and Sidney C. Wiggin. Dr. Barney was succeeded by Dr. Cotton as president, a position he held with success and enthusiasm until his death in 1938. Meetings were held at the homes of various members, with talks by such leading artists as C. Howard Walker and Cyrus Dallin.

The first exhibit after the formation of the Society was held October 15 to 20, 1934, at the Boston Medical Library, as part of the American College of Surgeons Convention. Once more, the contributions of the physicians yielded many more excellent works of art.

On June 3 to 5, 1935, for the first time, the Boston Physicians' Art Society was invited to hold an exhibit at the annual meeting of the Massachusetts Medical Society at the Hotel Statler, through the interest of the Chairman of the Committee of Arrangements, Dr. W. M. Shedden, for the pleasure and appreciation of the members of the Society and their families.

In 1938, the first exhibit of the American Physicians' Art Association was held in San Francisco as part of the annual meeting of the American Medical Association. Three hundred and fifty physician members exhibited, including several members of the Boston Physicians' Art Society. The first prize for an oil painting went to Dr. James C. Janney of Boston. Each year since then the American Physicians' Art Association exhibit has been a part of the annual meeting of the American Medical Association, over 1500 members having exhibited in the past two years.

A memorial exhibit in honor of Dr. Cotton was held at the Massachusetts Medical Society Annual Meeting in 1939, at the Hotel Bradford, at which time a bust of Dr. Cotton was shown, surrounded by Dr. Cotton's many contributions of art to the Society.

Dr. Fritz B. Talbot succeeded Dr. Cotton in the presidency of the Society.

World War II caused a lapse in the Society's activity until 1946, when Dr. J. Howard Means became president, with Dr. Somers Sturgis as secretary. Under Dr. Means the Boston Physicians' Art Society was reorganized as the Massachusetts Physicians' Art Society, to include all physicians of the state interested in all phases of art. Dr. James Janney, former president of the American Physicians' Art Association, succeeded Dr. Means, with Dr. Robert Buck as secretary.

In 1949, the Massachusetts Medical Society, at the suggestion of the Massachusetts Physicians' Art Society, voted to make the art exhibit an integral part of the annual meeting under the auspices of the Committee on Arrangements, as an added attraction for the benefit of the members and their families.

In 1951, Dr. Frederick C. Irving completed a successful year as president of the society, with Dr. William J. Shriber as secretary. The monthly meet-

ings were then held in the library of the Boston Lying-in Hospital.

The most successful exhibit to date was held at the Massachusetts Medical Society annual meeting, May 21 to 23, 1947, at the Hotel Statler, with 50 exhibitors.

In June, 1951, the writer was elected president, with Dr. Conrad Nobili, of Quincy, as secretary, to carry on the activities of the Society and encourage the physicians of Massachusetts to join them in "parergon" — their "work by the side of work."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38161

PRESENTATION OF CASE

First admission. A forty-three-year-old man was admitted to the hospital because of chest pain.

Four years before admission the patient had an attack of pneumonia and was treated with a sulfonamide drug. He made an uneventful recovery from the acute effects, but he never completely recovered his pre-illness well-being; he tired easily, was subject to many colds and gradually lost twenty pounds in weight. Two months prior to entry he was told he had an "unresolved pneumonia" and was put to bed and treated with sulfonamide pills for several weeks. He seemed to make an uneventful recovery, but three days before admission he developed pain in the left lower chest and left upper abdomen that was made worse by deep inspiration, coughing or lying on the left side.

He had had a chronic cough intermittently for four years. One year prior to entry he had been told he was anemic and had taken iron pills for a few months. He had worked in a rubber plant a few years before but had had no prolonged exposure to any known noxious substance.

Physical examination revealed a moderately thin man in no acute distress. There were a number of shotty glands in the posterior triangles of the neck. The chest and heart were negative. The abdomen was diffusely enlarged and a large firm tender mass could be felt filling the left upper quadrant down to the umbilicus and extending over to the right of the midline. No other organs or masses could be palpated in the abdomen.

The temperature was 98.6°F., the pulse 100 and the respirations 25. The blood pressure was 110 systolic, 75 diastolic.

A urine of specific gravity 1.030 was negative, and a stool specimen was guaiac negative. Examination of the blood revealed a red-cell count of 2,700,000, a hemoglobin of 8.5 gm. and a white-cell count of 2800, with 60 per cent neutrophils; a blood smear showed normal platelets, normal white cells with no immature forms and normocytic, normochromic red cells that showed moderate basophilia and marked variation in size and shape. The serum protein was 7.02 gm., the albumin 4.02, the globulin 3.0 gm., the nonprotein nitrogen 30 mg. and the uric acid 7.2 mg. per 100 cc. The prothrombin time was 23 seconds (normal, 17 seconds), and the bleeding and clotting times were normal. A cephalin-flocculation test was ++++ in twenty-four hours and a bromsulfalein test and a Congo red test were normal. A basal metabolic rate was +55. A barium-swallow examination showed a huge spleen displacing the stomach but no other abnormalities. Roentgenograms of the chest and long bones and the intravenous pyelogram were negative. A bone-marrow smear revealed a hyperplastic marrow with an erythroid-myeloid ratio of 1:1, some myeloid immaturity and some normoblastic hyperplasia; a bone-marrow section showed marked hyperplasia of the red-cell series, with a preponderance of normoblasts.

The patient was given 1000 cc. of whole blood and was discharged after twenty-one days feeling well; the hemoglobin on discharge was 15 gm. per 100 cc.

Second admission (ten months later) because of pneumonia. In the interval he was followed in the Out Patient Department. He felt fairly well and gradually became able to return to full-time work. The hemoglobin varied between 9 and 15 gm. and the spleen gradually became larger, finally reaching the iliac crest. Two months prior to entry, because of the massive size of the spleen, three x-ray treatments of 50 r each were given to the anterior spleen. Following this, the spleen shrank in size to a point where it was no longer prominent, the patient felt well and the hemoglobin rose from 11 gm. before treatment to 14.9 gm. two weeks after treatment. Ten days before admission he had the sudden

onset of pain in the right chest, chills, fever and cough productive of thick yellow sputum. He received oral penicillin at home, with some improvement, but his temperature remained around 103°F. and the chest pain persisted. He was unaware of any change in the color of his skin and had no other complaints.

Physical examination revealed a pale man who had considerable dyspnea and mild icterus of the skin and sclera. There was dullness, absent breath sounds, loud rales and rhonchi and a palpable audible friction rub over the right base. The edge of the enlarged, nontender spleen could be palpated just below the umbilicus, and the liver could be palpated 3 cm. below the costal margin.

The temperature was 103.3°F., the pulse 128 and the respirations 40. The blood pressure was 105 systolic, 55 diastolic.

The urine gave a ++ reaction for bile. A stool was guaiac negative. Examination of the blood showed a red-cell count of 1,400,000, a hemoglobin of 4.5 gm., a hematocrit of 14.5 per cent, a white-cell count of 6750, with 85 per cent neutrophils, and a reticulocyte count of 12.6 per cent. The bilirubin was 1.9 mg. direct and 3.3 mg. total, the alkaline phosphatase 6.5 units, the nonprotein nitrogen 25 mg. and the total protein 5.85 gm. per 100 cc., with an albumin-globulin ratio of 1.9. The prothrombin time was 20 seconds (normal, 14 seconds), the cephalin-flocculation test +++ in twenty-four hours. A culture of the sputum grew pneumococci. Roentgenograms of the chest showed an area of homogeneous density in the middle third of the right lung. X-ray films of the abdomen showed the spleen to be somewhat smaller in size than in the previous films and the liver to be somewhat enlarged. A bone-marrow smear showed normoblastic hyperplasia and a myeloid-erythroid ratio of 2:1, with no immaturity in the myeloid or erythroid series. Osmotic and mechanical fragilities of the red cells were slightly increased. Cold and warm agglutinin tests were negative. A Coombs test was positive to titer 1:128.

The patient was started on penicillin and given two transfusions. Within two days he was comfortable and had a normal temperature; he got along well and the jaundice cleared. On the fourteenth day an hour after a transfusion he had a shaking chill, developed a temperature of 103°F. and passed a dark port-wine-colored urine that contained no cells, was guaiac ++ and had a specific gravity of 1.015 and a pH of 6. After the chill had stopped he felt essentially well. The urine output dramatically increased, and by four hours after the transfusion the specific gravity of the urine was 1.002. Shortly after the transfusion the hematocrit was 29 per cent and the hemoglobin 9.5 gm.; the following day the hematocrit was 24 and the hemoglobin 8 gm. Recheck of the blood showed the patient to be type A, MN, CDe and the donor type A, MN, CDE, and cross match showed no evidence of incompatibility; tests using anti-E serum showed that the patient's blood contained a rather higher percentage of donor cells than would be expected.

The hemoglobin gradually rose to 10 gm. The patient felt well and was discharged on the twenty-second day; prior to discharge the Coombs test was positive in a titer of 1:16.

Third admission (two and a half years later). In the interval the patient was asymptomatic and able to do full-time work. The hemoglobin remained in the vicinity of 13 gm., the white-cell count varied between 1600 and 4000, the spleen remained enlarged and a Coombs test was weakly positive six months prior to entry. Three weeks before admission he had to quit work because of weakness. He noted aching in the ribs, hands and chest and, a few days before admission, weakness and swelling of the right hand. He had become anorexic, and in the two weeks prior to entry he became extremely weak; the hemoglobin was 10 gm. and the white-cell count 2600.

On physical examination the heart and lungs were negative. The liver was palpable 3 finger-breadths below the costal margin, and the edge of the spleen was palpated just above the inguinal ligament. The right hand and wrist were swollen, and there was tenderness of the distal ends of the metacarpals, the first phalanx, the right radius and the lower half of the right tibia.

The temperature was 100°F., the pulse 120 and the respirations 28. The blood pressure was 96 systolic, 55 diastolic.

The urine was negative. A two-hour urine specimen for urine urobilinogen contained 2.0 Ehrlich units. Examination of the blood revealed a red-cell count of 1,500,000, a hemoglobin of 5.8 gm., a hematocrit of 19 per cent, a white-cell count of 2050 per cu. mm., a platelet count of 22,000 per cu. mm. and a reticulocyte count of 1.2 per cent. A Coombs test was positive to titer 1:256. A test showed complement present in the serum. The bilirubin was 0.4 mg. direct and 1.1 mg. total, the total protein 5.6 gm. and the uric acid 5.6 mg. per 100 cc. The prothrombin time was 22 seconds (normal, 17 seconds), a cephalin-flocculation test ++ in twenty-four and forty-eight hours. Roentgenograms of the right hand, tibia and chest showed only soft-tissue swelling.

The patient was given ACTH, 100 mg. a day for twelve days, transfusions of washed red cells and four 50-r roentgen treatments to the spleen. There was some response to this therapy; the bone and joint pain and swelling subsided, and the hemoglobin rose to 8.0 gm. and the reticulocyte count to 3 per cent; the temperature remained elevated. On the nineteenth day a biopsy of iliac crest showed aplasia of the marrow. On the twentieth day he became slightly icteric and passed dark urine, which was guaiac ++, and the hemoglobin dropped to 4.5

gm.; spectroscopic examination of the serum showed a mixture of alkaline and neutral methemoglobins; that of the urine revealed a small trace of hemoglobin. A Coombs test was positive to titer 1:512. He received packed red cells and improved, his urine clearing within two days. A right acute suppurative otitis media was discovered; this responded to myringotomy and antibiotics. He was given oral cortisone, but this had little effect on his hematologic response or serum-complement level. He received numerous packed-red-cell transfusions, vitamin B_{12} and vitamin C. After each transfusion he passed dark urine for a short time. His course was slowly downhill; during the last three weeks his hemoglobin varied between 2.5 and 4.5 gm. He developed signs of congestive failure and died on the forty-third day.

Differential Diagnosis

Dr. Frank H. Gardner*: I saw this patient at Grand Rounds here about two and a half years ago, and I then made the statement that the diagnosis that I am going to make this morning was absolutely impossible. Within the last two and a half years we have observed these patients in some detail and have changed our concepts.

I am not going through this protocol step by step but shall point out some of the episodes I think are important. Each of the three episodes of pneumonia apparently tended to precipitate the onset of anemia. There was the history of work in a rubber plant, with some possible exposure to benzol. How well was this documented?

Dr. Benjamin Castleman: I believe the physicians did try to find out about exposure to toxins. Is that correct, Dr. Jacobson?

Dr. Bernard M. Jacobson: May I read the note of Dr. Frantz: "The patient works in a rubber factory. . .in the vicinity of a machine that cuts rubber tubing. He does not use any solvents now which contain benzol. There are now 'accelerators' used where he works, but he does not know what the composition of these are as they are patented. Prior to 1940 he worked in a plant which did use benzol, was a boss and was exposed only very intermittently, but this exposure lasted over a period of five years."

Dr. Gardner: He was admitted to the hospital for the first time with chest pain. He had distress from coughing on inspiration when lying on his left side and a large mass in the left upper quadrant. I presume the patient had a diaphragmatic type of pleural pain from a splenic infarct. This could exist without any physical signs and, if not too large would not necessarily give fever and leukocytosis. He had a moderate anemia, 8.5 gm., with variation in size and shape of the red cells and no abnormal white cells in the peripheral blood. These findings, together with the basal metabolic rate of +55, and slight elevation of uric acid, suggest a hypermetabolic state and, with the enlarged spleen, I am sure raised the question of lymphoma or aleukemic leukemia. I presume that these diagnoses led to the bone-marrow aspiration, in which only erythroid hyperplasia was found. I am anxious to know if the Pathology Department found any increase in megakaryocytes in the section at that time.

*Associate in medicine, Peter Bent Brigham Hospital.

Dr. Castleman: The sections that were made at the time were quite a puzzle; the first diagnosis that we made was lymphatic leukemia, because we saw many lymphocytes, but we finally came to the conclusion that it was probably some form of red-cell hyperplasia. There were lymphocytes in the bone marrow, but it is quite possible that they were part of lymphoid centers that are occasionally seen in any abnormal marrow.

Dr. Gardner: But the megakaryocytes were not startling at any time?

Dr. Castleman: No.

Dr. Gardner: The radiation therapy given for progressive splenomegaly resulted in a decrease in the size of the spleen and an increase in the hemoglobin from 11 to 14.9 gm. The erythroid hyperplasia of the bone marrow and the polychromatophilia of the peripheral blood certainly suggest a hemolytic process. Even though no reticulocyte count was made, I assume he had some reticulocytosis. The decrease in size of the spleen associated with a possible lymphoma or neoplasm probably lessened the amount of red-cell destruction that could occur in the large spleen.

During the second admission the patient had pneumococcal pneumonia and anemia. Further evidence that the anemia was hemolytic was the increased red-cell fragilities, the positive Coombs test, the elevated bilirubin, the icterus of scleras and skin and the normoblastic hyperplasia of the bone marrow. In passing I should mention that I have not considered the cephalin-flocculation test with much emphasis; patients who show a positive Coombs test may have in the peripheral blood abnormal flocculation tests that ordinarily may be used to measure abnormal proteins in liver disease; a great many of these patients have abnormal Wassermann reactions, which disappear after splenectomy for hemolytic jaundice.

At the time of the second admission I saw the patient. I have reviewed recently the rather faded blood smear made during that admission and noted 6 per cent metamyelocytes, 3 per cent myelocytes, the presence of normoblasts and a marked variation in size and shape of the red cells without hypochromia. I did not pay much attention to the red-cell changes then, but now I believe them to be important, in view of the cases we have studied in the last few years. Although these early white cells may exist in any severe hemolytic anemia, — I am sure on the Pediatric Service it is seen again and

again, — it is rare in adults. The marked variation in size and shape of the red cells is not part of the hemolytic process *per se*. In the presence of a large spleen, no adenopathy and the leukoerythroblastic blood picture, a clinical diagnosis of myeloid metaplasia of the spleen would have to be made. The importance of a variation in size and shape of the red cells without hypochromia has been brought out by Miss Daland at the Thorndike Laboratory, who has seen many of these cases in the past ten years. I do not know of any other anemic state with which this condition could be confused. The variations in size and shape of red cells occur with iron-deficiency anemias, the thalassemias and sickle-cell disease. However, all these anemias show hypochromia of the red cells.

One would have to consider how myeloid metaplasia could be correlated with the extreme hyperplasia of the bone marrow. In the study of myeloid metaplasia that Jackson, Parker and Lemon[1] published, bone marrows of any type might be obtained on random sampling; they classified marrow findings as normal, hyperplastic and fibrotic. Block and Jacobson[2] comment that in some of their marrow aspirations there was a fibromyxomatous type of degeneration. Since they do not show any pictures, I assume that term merely means an aplastic type of marrow with a few histiocytes and a few early forms of red and white cells present. Aside from these classifications of bone-marrow findings, myeloid metaplasia can exist secondarily from other causes that interfere with bone-marrow function. Certainly the diagnosis of lymphocytic leukemia Dr. Castleman mentioned should be considered as part of the differential diagnosis of a secondary type of myeloid metaplasia. Among the various tumors that have been incriminated in diffuse replacement of bone marrow are Hodgkin's disease, lymphosarcoma, carcinoma of the prostate and other diffuse metastatic carcinomas from breast, thyroid and kidney. Granulomas, especially tuberculosis of a miliary type that has healed, have been reported. Jackson, Parker and Lemon[1] reported their first series, which they named agnogenic myeloid metaplasia, twelve years ago; their first case was a woman who had very severe hemolytic jaundice, according to their interpretations at that time. She, like this man, had a slight increase in osmotic fragility, an elevated icterus and reticulocytosis and had a splenectomy for hemolytic jaundice.

For two and a half years the patient maintained himself without complication or further hemolysis. It is important in evaluating this diagnosis to realize that patients with myeloid metaplasia can live for ten, fifteen or twenty-five years with only splenomegaly and intermittent episodes of complaints from the size of the spleen. This patient's hemolytic episodes were always associated with some acute infection that might have acted as a trigger mechanism. Certainly in children with acquired hemolytic anemia, the exacerbations follow infections, pulmonary infections especially. Whether or not that played a role here I cannot tell with certainty.

On the last admission the patient had a catastrophic type of hemolysis. This case is very similar to one reported ten years ago by Brewster.[3] His patient had severe fulminating hemolysis that could not be controlled with blood transfusions; on splenectomy myeloid metaplasia was demonstrated. The patient under discussion had severe destruction of red cells evidenced by hemoglobinemia and hemoglobinuria after transfusions. It is disappointing that the anemia did not respond to steroid hormones, in view of the favorable results we have had in patients with acquired hemolytic anemia and a positive Coombs test. I do not know the effect of the roentgen therapy to his spleen. He had ACTH for twelve days, with the improvement in the aching and swelling of the soft tissues that I will have to assume was evidence of some response. This drug was given intramuscularly; we know that some patients have not responded to intramuscular ACTH and have responded to intravenous ACTH.

What dosages of cortisone did this patient have? Unless 300 or 400 gm. a day was used, I probably cannot evaluate it.

DR. JACOBSON: It was given during the last ten days of life. The actual dosage that is listed here is 25 mg. four times a day for three days, increasing to 75 mg. three times a day.

DR. GARDNER: Heroic dosage would be almost imperative if one wanted to determine whether it was adequately used.

Before concluding, I should like to see the x-ray films of the bones. Were there any changes in the cortex of the long bones?

DR. STANLEY M. WYMAN: The early films show the initial size of the spleen, which was tremendous, extending down to the iliac crest and displacing the stomach far toward the right. The films taken during the last admission, when the patient had pain in the extremities, demonstrate perhaps some increase in the expected amount of density in the distal portion of the long bones, but that is very minimal and perhaps questionable. I think they may be considered grossly normal.

DR. GARDNER: In the literature physicians have commented on aching over multiple joints in patients with myeloid metaplasia without much explanation. We biopsied the tibia of a man with myeloid metaplasia whose pain was beyond control with analgesics. The whole area of biopsy was replaced by fibrous tissue. We later found the same fibrous-tissue replacement of marrow in the sternum and iliac crest. He was given intensive x-ray therapy over the lower extremities, with complete remission of the pain. The pain was attributed to medullary expansion of fibrous tissue. I suspect that possibly some such disorder may have been a factor here;

I am not implying that it necessarily has to have been fibrosis. The bone marrow during the last admission showed aplasia; I do not know whether this means just absence of cellular forms or whether it actually could contribute to some expansion of the medullary cavity.

We have had to change our minds about mechanisms in this disease. The last three patients with this condition our clinic has studied have had a hemolytic anemia at a time when we thought they were relatively asymptomatic in the course of myeloid metaplasia. These patients have had shortened red-cell-survival times, positive Coombs tests and no gross abnormalities in their red-cell fragilities. Two out of three that we have been able to treat have responded well to adrenal-steroid hormones with increased blood values. We now assume that myeloid metaplasia has a factor of acquired hemolytic anemia when the patient has entered the anemia phase. I believe this patient had an acquired hemolytic anemia since his first admission that was accentuated by infections.

Terminally this patient had all evidence of an aplastic anemia. It is difficult to understand why a spleen that had been contributing to red-cell and white-cell production for a period of years suddenly should completely lose that ability. I suspect that some of the inhibition of red-cell production can be attributed to his immediate infection. I can certainly see what a terrible dilemma occurred in treating this patient with large doses of steroid in the presence of active infection — the possibility of dissemination of infection versus the need to control hemolysis.

My final diagnoses are myeloid metaplasia of the spleen with aplasia of the bone marrow, severe acquired hemolytic anemia and otitis media.

Dr. Morton Grove-Rasmussen: During the second admission this patient had a hemolytic crisis following the transfusion of 500 cc. of blood; the bloods of the patient and the donor were rechecked and found compatible. Differential agglutination experiments strongly suggested that the patient had been hemolyzing his own cells more than the cells of the donor. The serum of the patient did not contain complement in any measurable amount, whereas the plasma of the donor blood contained a normal amount of complement. It was suggested at that time that the hemolytic crises following the transfusion of whole blood may have been due to the fact that plasma-containing complement had been transfused into a patient whose serum contained no complement but whose red cells were coated with antibodies and therefore were giving a positive Coombs test. Two years later the patient's serum was rechecked for complement and no measurable amount of this substance was found. At that time the patient's condition was relatively good and his hemoglobin was close to normal, but his red cells were still giving a positive Coombs test. During the last admission the patient was more or less constantly hemolyzing the red cells. The serum complement was checked several times before and after treatment with cortisone and the complement was found to be normal or probably slightly decreased. It is known from experiments with guinea pigs[4] that ACTH and cortisone can produce a fall in complement in the blood, but we were not able to find an appreciable decrease in the amount of complement during this patient's treatment with cortisone. Whether the patient would have stopped hemolyzing the red cells if the complement had been decreased to a low amount I do not know, but he was undoubtedly much better at the time when we could find no complement in the serum.

In this connection it is worth while to mention the experiments that Christian and others[5] have carried out with dogs, giving them successive transfusions of incompatible dog erythrocytes. They found that the rate of hemolysis was influenced by the initial titers of both antibody and complement. Available complement appeared to limit the rate of destruction of incompatible donated cells in dogs with high antibody titer, whereas on the other hand in the presence of adequate complement the rate of hemolysis was limited by the disappearance of antibody when the initial titer of antibody was low.

Dr. Jacobson: I listened with pleasure to Dr. Gardner's extended discussion of this case when the patient was presented at Medical Grand Rounds during the second admission. At that time Dr. Gardner would not commit himself about the fundamental etiology of the patient's splenomegaly but did discuss the acquired hemolytic anemia and the reason for making this diagnosis at that time.

I saw this patient on every admission. As you gather from the protocol, he had radiation therapy on several occasions. It should be emphasized that the patient was better after at least two of the courses of radiation; the hemoglobin came up, the spleen shrank a little; he felt better and continued in fairly good shape for a long time.

During the second admission I believe he did not have agnogenic myeloid metaplasia. To be sure, we did see a few myelocytes and a few normoblasts together with a few reticulocytes in the peripheral blood, but this was during the hemolytic phase. At that time I believed that the fundamental disease of the large spleen was undetermined and that a diagnosis should be made before proceeding with splenectomy or radiation. I suggested an open biopsy of the spleen, with splenectomy, if the spleen did not show myeloid metaplasia — without splenectomy if it did show myeloid metaplasia. I based my opinion at that time largely on the now historic monograph by Hickling,[6] which preceded the Boston workers' report by several years. He pointed out that of 27 patients with myeloid metaplasia, or, as he calls it, chronic nonleukemic myelosis, subjected to splenectomy, 17 died within three

months regardless of whether their marrow was normal, hyperplastic or hypoplastic. This open biopsy was not performed. I see nothing in the later protocol to change my opinion that the disease of the spleen remained unknown; perhaps it was sarcoidosis, lymphoma or Banti's fibrosis. There is no question, of course, that infection precipitated hemolytic episodes.

A PHYSICIAN: I wonder if Dr. Gardner could estimate the incidence of transfusion reaction in persons with a hemolytic process of that type, and if he would explain the so-called plasma reaction that Dr. Dameshek talks about.

DR. GARDNER: I cannot give you an incidence of hemolytic reaction. Certainly some patients with acquired idiopathic hemolytic anemia or with hemolytic anemia associated with myeloid metaplasia do have hemolytic reactions in the sense of destroying red cells. In the groups with liver disease it is serious because the patients are not able to tolerate the pigment metabolism associated with the destruction. The patients without liver disease have no trouble; they merely become more jaundiced, and when the disease is severe they have hemoglobinemia and hemoglobinuria, but they usually do not have trouble.

The second problem, the plasma factors, is one that is ill defined and one that I do not understand. In patients who have had fever and chills from previous transfusions, we remove the plasma from the blood before transfusion. For a while we used blood collected through resin columns without using anticoagulant solution. We thought that did away with reactions. However, after six or eight of those transfusions, we had a reaction. I do not know that anyone can say exactly what the cause is.

A PHYSICIAN: What is your opinion of giving transfusions to patients with cirrhosis, splenomegaly and jaundice in the presence of a hemolytic process?

DR. GARDNER: Patients with hemolysis and that type of liver disease usually show reticulocytosis. If they show reticulocytosis and possibly an increased urobilinogen, I should be most hesitant, certainly cautious, about giving transfusion. We give them small transfusions — about 200 cc. at a time.

A PHYSICIAN: Is there any point in giving steroids with it?

DR. GARDNER: When we were doing those studies no steroids were available, so I do not know whether it would do any good or not.

CLINICAL DIAGNOSES

Congestive heart failure.
Acquired hemolytic anemia.
Agnogenic myeloid metaplasia.

DR. GARDNER'S DIAGNOSES

Myeloid metaplasia of the spleen.
Aplasia of the bone marrow.
Severe acquired hemolytic jaundice.
Otitis media.

ANATOMICAL DIAGNOSES

Myeloid metaplasia of spleen.
Histiocytic leukemia involving bone marrow, lymph nodes and pituitary.
(*Hemolytic jaundice.*)

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy here showed, as was expected, a huge spleen, weighing over 1600 gm. — as large a spleen as you see in any condition except myelogenous leukemia. Occasionally a Banti spleen may be that large.

DR. JACOBSON: We had one Banti spleen that weighed 3200 gm.

DR. CASTLEMAN: There were many adhesions over the spleen, apparently from old infarcts, and in the gross the spleen seemed quite fibrotic in places. The lymph nodes throughout the body seemed larger than normal. Outside of that, one could not make any diagnosis in the gross. The marrow taken from the vertebras, the sternum, rib and femur were all red and not fatty, so that there was certainly evidence of some activity in the marrow. The iliac bone-marrow biopsy called aplastic could not have been an adequate sample.

Microscopically, in the sinusoids of the spleen were large cells with pale nuclei that were characteristic of the red-cell series — that is, megaloblasts. There were also large numbers of normoblasts and a great deal of fibrosis. This is the characteristic picture of so-called myeloid metaplasia; if I saw that slide and did not know anything about the patient, I would suspect that the patient had been exposed to benzol. It is quite possible that this was the etiology of the myeloid metaplasia of the spleen in this case. There were other cells, some of which looked like histiocytes, which are not uncommon in the spleen, so we did not pay too much attention to them.

The vertebral bone marrow was free from fat cells and was packed with cells suggestive under low magnification of either marked hyperplasia of some cell or leukemia. When studied under higher magnifications, the characteristic cell was spindle-shaped, sometimes horseshoe-shaped, with pale irregular nuclei, and was characteristic of the reticulum cell, or what Dr. Frederic Parker likes to call the histiocyte. Looking at this bone marrow alone, I would call this a reticulum-cell sarcoma or histiocytic leukemia. Since the same bone-marrow picture was present in the femur, sternum and the ribs, we would then have to make a diagnosis of histiocytic leukemia. All the lymph nodes throughout the body showed these same cells, with increase in the reticulum around each of them, which is evidence for reticulum-cell sarcoma. Dr. Parker, who examined these slides, would call this a histiocytic or clasmatocytic type of leukemia; he does not like

to make the diagnosis of reticulum-cell sarcoma without finding large tumor masses. Dr. Robb-Smith, in England, would probably call this a non-lipid reticulosis. A random section through the pituitary revealed an island of these same cells in the posterior lobe, so that we had evidence of infiltration of other organs — as a matter of fact, it was the only other organ involved. This patient, therefore, had two diseases, myeloid metaplasia, which I do not think you can get away from, and leukemia. The myeloid metaplasia would have to be the agnogenic type, — that is, the type often associated with benzol poisoning, — and not the type secondary to marrow replacement. The latter type never produces a large spleen, as large as 1600 gm. — they may weigh 500 to 800 gm. I think I have to end by saying that the patient had a myeloid metaplasia probably due to the benzol and, as do so many of the patients exposed to benzol, later developed a leukemia — a leukemia of the histiocytic type.

DR. GARDNER: The liver?

DR. CASTLEMAN: The liver showed none of these cells; it appeared normal.

DR. GARDNER: The Thorndike Laboratory has studied one patient who had myeloid metaplasia for twenty-five years and then finally developed what I thought was myelogenous leukemia. Many workers think that myeloid metaplasia is a variant of leukemia. Other authorities believe that two separate diagnoses must be made.

DR. CASTLEMAN: We have had two or three cases of myeloid metaplasia associated with intoxication with benzene in which leukemia has developed, one myelogenous and one lymphocytic, but this is the first time we have seen it with this type of leukemia.

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CASE 38162

PRESENTATION OF CASE

A sixty-five-year-old woman was admitted to the hospital because of abdominal pain.

Twelve days prior to entry she became chilled while waiting for a bus, and the chill seemed to "settle in her stomach." The following day she felt weak and developed crampy pain in the left lower quadrant, which was relieved by lying down; her abdomen felt sore and "hard." For the next two days, during which she remained in bed, she had increased bowel movements (up to three to four times a day), with mushy stools and tenesmus, and vomited once. Later her bowel movements reverted "nearly to normal," but the tenesmus persisted. Eight days prior to admission she visited a physician, who prescribed paregoric and some white pills. She had no relief from these, felt tired and continued to have vague crampy abdominal pain; for three days prior to admission the pain was most severe in the left lower quadrant and kept her awake at night. During the few days before admission she noted that her abdomen was enlarged. The pain had been unaffected by bowel movements, but mild burning and cramps accompanied urination. There had been no melena, constipation, weight loss or vaginal discharge or bleeding.

Fifteen years prior to admission, during hospitalization for pneumonia and pleuritis, she was found to have positive serologic tests on both blood and spinal fluid and received antisyphilitic treatment for two years. Nine years before admission she was seen in the Medical Clinic because of a right trigeminal neuralgia that was relieved by alcohol injection. After this she received further antisyphilitic treatment — at first heavy metals and then penicillin. At the termination of this treatment and at regular subsequent follow-ups this disease was considered arrested.

Physical examination revealed an obese woman in no acute distress. The pupils reacted to light and accommodation. The lungs were clear. The heart was slightly enlarged to the left. A Grade II systolic murmur was heard over the base of the heart, along the left sternal border and at the apex. The abdomen was markedly distended and was tympanitic except for definite dullness in the left flank and suprapubic area. There was no definite spasm. There was good peristalsis throughout. A tender lobulated mass filled the pelvis and extended high into the left lower quadrant, almost to the level of the umbilicus. The upper part of this mass felt distinctly cystic and to some extent could be moved and ballotted. Pelvic examination revealed a small cervix and large fixed pelvic masses on both right and left sides, the latter mass being twice the size of the former. The fundus could not definitely be made out. By rectal examination the mass sat on top of the pelvic floor on the rectum.

The temperature was 99°F, the pulse 80 and the respirations 23. The blood pressure was 150 systolic, 80 diastolic.

The urine had a specific gravity of 1.035 and was normal. Examination of the blood showed a hemoglobin of 12.6 gm. and a white-cell count of 16,000. The nonprotein nitrogen was 15 mg. and the total protein 5.99 gm. per 100 cc. A blood Hinton test was positive. A stool guaiac test was negative. Roentgenograms of the chest showed a slightly

enlarged heart, a slightly tortuous aorta and clear lung fields. A plain film of the abdomen revealed generalized haziness, scattered gas in both large and small bowel and a suggestion of a soft-tissue mass in the lower abdomen. On barium-enema examination an obstruction was encountered in the sigmoid; a small amount of barium trickled through the sigmoid into the midportion of the descending colon, but examination of the proximal colon was not possible (Fig. 1). There was good emptying and

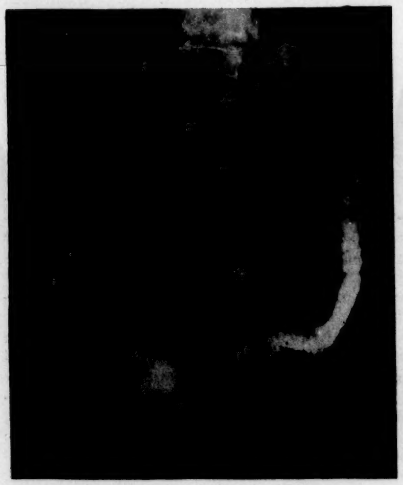

FIGURE 1.

normal mucosal folds throughout the part visualized. The sigmoid was flattened and immobile and the rectum was displaced to the right. Intravenous pyelogram showed a large amount of gas in the large bowel and a small amount in the small bowel. The renal outlines were normal, and contrast material appeared promptly in good concentration, outlining slightly dilated upper urinary passages. There was slight embarrassment of urinary drainage on both sides, most marked on the left. The bladder shadow was deformed by the mass in the lower abdomen (Fig. 2). An electrocardiogram suggested left-ventricular hypertrophy. A vaginal smear was "doubtful for tumor cells."

Shortly after admission the patient's temperature rose to 101°F. This responded well to penicillin and streptomycin, and by the fifth day she was afebrile. On the seventh day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARSHALL K. BARTLETT*: Dr. Wyman, may I see the x-ray films?

DR. STANLEY M. WYMAN: The first films of the chest show enlargement of the heart, chiefly of the left ventricle, and a slightly tortuous aorta. The films selected from the pyelogram show normal upper urinary passages and some embarrassment of the left ureter that is best seen on the film from the barium-enema examination showing the ureter passing over the region where this rather large mass can be seen in the central pelvis. The mass measures perhaps 8 to 10 cm. in diameter (Fig. 2). There is evidence of the old metallic injections in both buttocks. The colon itself shows no intrinsic disease but is compressed in the midsigmoid region (Fig. 1); there is a definite suggestion that there is either a

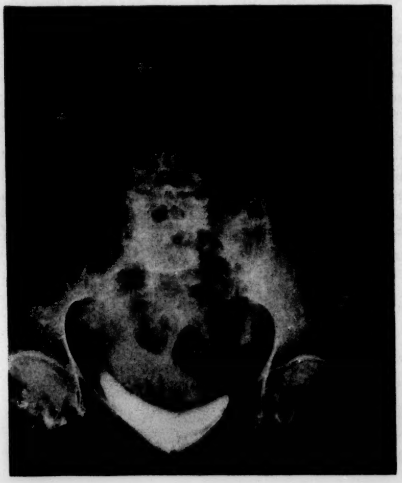

FIGURE 2.

continuation of this mass that can be seen in the lower pelvis or a second mass lying above it and compressing the colon at this point. I do not think there is much more that I can say about this. There is some gas in loops of small bowel but no frank obstruction. There is perhaps some element of small-bowel embarrassment. I do not see localized bone destruction.

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DR. BARTLETT: What you can see of the mucosal pattern, both in the narrowed area and above, appears normal?

DR. WYMAN: Yes; I do not see any evidence of diverticulosis, a filling defect or an ulceration.

DR. BARTLETT: I shall start the discussion with the known facts and progress from there. There is no question that this patient had some process causing incomplete obstruction of the sigmoid. The history, the type of pain she had, the change in the bowel habits and the distended abdomen seem to fit into the picture of at least partial obstruction, and it has been localized as being in the sigmoid. In addition to that, there is evidence of some inflammatory process, related to the process that was obstructing the sigmoid. In favor of this are the fever, the elevated white-cell count and the tenderness of the mass. All I have to do is find a process that will fill those requirements and give this x-ray picture.

Was this a mass within the bowel or was it an extrinsic process producing pressure on the bowel? The extrinsic lesions likely to cause pressure would, I suppose, be those arising from the pelvic viscera. It is unlikely that she would have an extensive carcinoma of the cervix or endometrium without having some external manifestation in the form of vaginal discharge or bleeding; the vaginal smear was only doubtful. These masses could represent lesions in the ovary with extrinsic pressure on the colon. On the other hand, I think secondary infection of that type of process is rather unusual; it certainly would disturb me somewhat in holding out for that diagnosis. If it proved to be a process extrinsic to the bowel, the most likely lesion would be a neoplasm of the ovary.

Among the lesions intrinsic to the bowel, the first thing that comes to mind is carcinoma. That, of course, perforates not too infrequently and could produce a pelvic mass of this type, with fever, tenderness and the other signs of inflammation. This patient, however, has had no rectal bleeding, which I think she should have had with a tumor of this size. The only guaiac test reported was negative. More disturbing than that, perhaps, is that the mucosal pattern, as seen by barium-enema examination, was intact throughout that narrowed area. Although that does not rule out carcinoma, I think it is rather unlikely that with a tumor of this extent no destruction of the mucosa in the sigmoid would be demonstrable by x-ray examination.

What other neoplasm should I consider? Although I have seen lymphoma in the small bowel obstruct and perforate, I have never seen it in the colon. I suppose it must be considered, but on the basis of my experience it would be an outside possibility. I have seen a carcinoid in the rectum, but it is doubtful that a carcinoid would attain this size; at least, those that I have seen have not been of this size except when they were in the terminal ileum and involved the mesentery. I think it unlikely that a carcinoid would become secondarily infected. Those objections and the rarity of this type of lesion lead me away from serious consideration of it.

There is quite a bit of information in the protocol about syphilis. Did she by any chance have a syphilitic lesion? I am completely at a loss there, as I have never seen anything due to syphilis in the colon that could vaguely resemble this picture.

The commonest nonmalignant inflammatory lesion in this area is diverticulitis of the sigmoid. I think the picture is compatible with this diagnosis, except for the lack of diverticula in the x-ray picture. That does not rule it out, since if the diverticula are limited to the inflamed area they may not fill with barium at this stage of the disease. Certainly a lesion that shows considerable narrowing from below by x-ray examination or even complete obstruction and yet a clinical obstruction that was transient in its manifestations is compatible with diverticulitis — in fact, is rather like it. The negative guaiac test is a little more compatible with diverticulitis than with the ordinary carcinoma of the sigmoid. The thing that discourages me most is the lack of any other visible diverticula. Since this is a clinicopathological case, I may well end up with some rare condition, but I see no way to play this except to consider it on its own merits, and it seems to me that the most likely condition is an inflammatory process, which is probably diverticulitis despite the things against it in this picture, with a considerable inflammatory process around it causing narrowing of the colon. As second best I would think of carcinoma of the colon. Of the extrinsic lesions, I think the best bet would be ovarian carcinoma, although it is not so good a choice as the first two.

A PHYSICIAN: How about an ovarian cyst, Dr. Bartlett?

DR. BARTLETT: If it was a cyst, I think it was malignant, because of the degree of embarrassment of the sigmoid. I think it is rather unusual for such

a lesion to develop the signs of inflammation that this patient had.

A PHYSICIAN: The hemoglobin was about normal.

A STUDENT: What about the fact that there were relatively large fixed masses on both sides of the pelvis?

DR. BARTLETT: Two distinct masses would be against a process such as diverticulitis or carcinoma, but I am not at all sure that this was not one mass extending across the pelvis. If there were two masses, then I should be in favor of a bilateral ovarian process.

DR. WYMAN: I should like to emphasize that this is a very round mass down in the pelvis and that possibly there is another one above it that is embarrassing the left ureter; I would lean away from the possibility of diverticulitis without seeing some diverticula, and I do not think I have ever seen a carcinoma of the colon produce that large an extrinsic mass without some evidence of it in the lumen. I would like to put in a vote for ovarian cyst, possibly one with a twisted pedicle and inflammatory change.

DR. BARTLETT: I think Dr. Wyman has made a very good point. The onset of this disease, with the emphasis on the bowel symptoms, seemed to me to be against its being an ovarian cyst with embarrassed blood supply. Her initial symptoms were those of pain and change of bowel habits, which, however, did subside after a few days.

DR. R. H. FENNELL: Dr. Edwards, would you tell us the opinion on the ward?

DR. STERLING EDWARDS: We thought that the process was most likely ovarian carcinoma, with multiple metastases. Our opinion was based on the negative x-ray examination of the urinary tract and colon, and on the cystic feeling of the mass.

DR. BARTLETT: Was the mass a single one?

DR. EDWARDS: It seemed to be a single lesion.

CLINICAL DIAGNOSIS

Ovarian carcinoma with metastases.

DR. BARTLETT'S DIAGNOSIS

Diverticulitis of sigmoid.
?Carcinoma of sigmoid.
?Carcinoma of ovary.

ANATOMICAL DIAGNOSIS

Gangrenous appendicitis, with rupture and bilateral pelvic abscess formation.

PATHOLOGICAL DISCUSSION

DR. EDWARDS: At operation the peritoneum was entered through a lower-abdominal incision. A moderate amount of serous fluid was aspirated. It was immediately apparent that the palpable mass was small bowel matted with thick recent adhesions. On separating these adhesions down in the left pelvis we came on a large abscess cavity. In the right pelvis a second large abscess cavity was encountered, and after aspiration of pus a ruptured appendiceal stump was found at the bottom. This was obviously the site of the disease. The stump was removed and the abdomen closed without drainage. The patient did well postoperatively on antibiotics.

DR. FENNELL: The material that we received was fragments of yellowish friable material not recognizable as appendix. On microscopical examination it showed gangrenous appendicitis.

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*On leave of absence with the Armed Forces.
†Representing the New Hampshire Medical Society.

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THE DISTRICT MEDICAL PUBLICATION

A branch of journalism so serviceable to the medical practitioner as almost to remind one of the New England town meeting is represented by the periodicals published in the interests of the district medical society. In referring to these publications one need make no distinctions of comparative value on the basis of national, state and local "levels," for the same individuals who make up the platoon make up also the army. It is obvious that the bulletin of the district medical society serves an intimate function that the national or even the state journal can hardly hope to duplicate, however well disposed those who conduct it may be.

Of the nineteen districts that comprise the Massachusetts Medical Society, five have already found it profitable to publish bulletins. These appear at varying intervals of time, but all serve the same general purpose of maintaining the bonds that unite physicians in their common enterprises. In addition to these five, the Greater Lawrence Medical Association publishes its own *Cardiograph*, "a recording of news items of interest" and the only regular bulletin appearing in Essex County.

To summarize them briefly, the *Worcester Medical News*, now in its fourteenth volume, appears at monthly intervals from September to May. The *Hampden Hippocrat*, with its seventh volume in current publication, is issued shortly before each meeting of the Council of the parent society. The *Bulletin of the Middlesex East District Medical Society* appears five times a year, prior to the meetings of the district society — Volume 4 is now in publication — and the *Worcester North Bulletin*, in its third year, is published quarterly. All contain news of the district, frequently an editorial and sometimes a clinical or scientific article of local authorship.

Unhampered by geographical restrictions, the something more than semi-independent *Norfolk Medical News*, distributed without cost to the entire fellowship of the *Massachusetts Medical Society*, occupies a unique position in current district-society literature. Published ten times a year, with a somewhat tenuous relation to the Norfolk District Medical Society as a whole, it has chosen as its function the spontaneous expression of editorial opinion on a variety of current topics; this has gained it wide recognition, due to its crusading zeal and persuasive eloquence.

Since free expression of opinion is a privilege inherent in the process of democratic evolution, the more orthodox district publications should be encouraged to enter the arena where affairs concerning the physician and his interests are discussed. The open forum, as fundamental to the concept of liberty as the town meeting, might well become a feature of their columns, including an editorial consideration of controversial subjects. It goes without saying that those comments will carry the greatest weight that bear the mark of considered opinion and an open mind, and that, sparing of adverse criticism, place their emphasis on thoughtful constructive analysis.

PHYSICIAN AS CITIZEN

THE letter from Dr. Chasen published elsewhere in this issue of the *Journal* reminds one that the moral and ethical level on which the profession of politics is practiced reflects in general the standards of those who participate in it. The medical profession, always wary of the political "taint," has tended more and more to follow the advice given by Oliver Wendell Holmes, to a graduating class in medicine, to avoid the muddy stream of politics.

This advice, however, was applied to another time, when another concept of professional deportment and professional relations was accepted. It applied to an era in which correct professional conduct was confined to a restricted albeit a vital role — when a physician was judged more by his personal relations with his patients than by any political type of service to his community. Those men of ability and high standards who made a profession of politics were considered to be making unusual sacrifices in the common cause, and physicians were not generally expected to be numbered among them.

It must not be supposed, nevertheless, that the physician who was interested in the life of his community was always permitted to continue along any sequestered professional pathway. His community was likely to seek him out and draft his services for a local need, whether on the board of health or the school committee or in some loftier position, even including the mayor's office. Such service was, and is, more often on a local level, at which personality exerts its influence, than in a state or national capacity.

Today, more than ever, with political pressures being exerted on the medical profession and with the scope of professional services and professional interests ever widening, the physician must be more ready than hitherto to serve where his qualifications are evident.

Incumbent on every physician, whether or not he is personally suited for office, is the discharge of the obligations that suffrage has laid on him. Inescapably linked to a moral and ethical leadership that his attainments and the sanctity of his services have given him, the physician is faced also with the responsibility of exercising leadership in the plainest and most obvious duty of citizenship — that of going to the polls and casting his ballot.

THE BOSTON GUILD FOR THE HARD OF HEARING

MUCH can still be done for the patient with permanently impaired hearing when the family physician and the otologist find that there is no medical cure. For advice on hearing aids, for auditory training and lessons in lipreading, for guidance in his education and his work, and for help in overcoming the psychologic effects of his condition he can be directed to highly skilled persons who have been trained to help him. This help can be obtained through the Boston Guild for the Hard of Hearing.

The Boston Guild for the Hard of Hearing is a clearing house for all nonmedical information for the hearing-impaired adult or child and for those who are interested in helping them. All questions pertaining to the hard of hearing can be answered at this social agency, which offers a complete rehabilitation program for the patient after medical clearance. The Guild stands ready to assist anyone in need of help to overcome a hearing handicap.

Among the specific services that the Guild offers the patient is the hearing-aid consultation service. This gives the person who is hard of hearing the opportunity of testing the newest models that have been accepted by the American Medical Association and approved by the American Hearing Society. The service is strictly noncommercial. The Guild has no bias concerning hearing aids, is not interested in sales and sells nothing. The Guild takes the position that there is no "best" hearing aid but that the person who needs an aid should find the one best suited to his degree and kind of hearing loss.

The hearing aid is used to best advantage only when supplemented with lipreading, which gives meaning to the amplified sounds. Afternoon and evening classes are therefore held at the Guild for individual and group instruction in lipreading. Auditory training is another aid to the hard of hearing offered at the Guild; this is a method of teaching the affected person to listen more attentively and to recognize the noises and sounds about him. This training is vital in the effective adjustment of new hearing-aid users.

The Guild offers a program for every age group, with special attention given to nursery-age youngsters. Remarkable advance has been made in voice and speech training of those whose hearing has become impaired before a speech pattern has been developed.

The Guild, open to all, is a Red Feather service that is in constant touch with Boston's network of public and private social agencies and shares in the over-all planning and research of the United Community Services of Greater Boston.

The American Hearing Society, of which the Boston Guild for the Hard of Hearing is one of several New England chapters, is sponsoring a National Hearing Week from May 4 to May 10. This dedication should focus the attention of both the medical profession and the public on the vital social problems caused by hearing impairment.

CRYSTALLOID–COLLOID RELATIONS

THE paper on urinary colloids in kidney-stone formation, by Butt and Hauser, which appears elsewhere in this issue of the *Journal*, refers to a problem of considerable interest to the human race.

Although much has been revealed concerning the causative factors in the formation of stone in the urinary tract, many of the detailed physical and chemical factors are still little understood. Among these, the crystalloid-colloid relations in urine have long been considered of possible importance in the etiology of calculi, but no completely convincing work has been published to settle entirely this still open question.

The evidence that these authors have presented concerning the role of hyaluronidase as an agent in influencing colloid-crystalloid balance although not conclusive is of great interest, and should stimulate further laboratory and clinical experimentation.

A report is circulating that at the hospital of Santa Theresa, at Vienna, the surgeons are performing operations with a platina wire, heated intensely by a powerful electrical battery. The knife, it is supposed, is laid aside.

Boston M. & S. J., *April 21, 1852*

MASSACHUSETTS MEDICAL SOCIETY

POSTGRADUATE LECTURE COURSE

John Ware Hall
Boston Medical Library
8 Fenway, Boston

Wednesday, April 23. CHEST DISEASES. Chairmen: Drs. Carlton R. Souders and Richard H. Overholt.

4:00–4:30 p.m. **The Management of Esophageal Lesions.** Dr. Herbert D. Adams.

4:30–5:00 p.m. **Modern Aspects of the Surgical Treatment of Tuberculosis.** Dr. John W. Strieder.

5:00–5:30 p.m. **An Evaluation of X-Ray Therapy for Intrathoracic Lesions.** Dr. Laurence L. Robbins.

5:30–6:30 p.m. **The Cancer Potential of Silent Pulmonary Shadows.** Dr. Richard H. Overholt.

Monday, April 28. PEDIATRICS. Chairmen: Drs. Nathan B. Talbot and James M. Baty.

7:00–7:25 p.m. **Recognition of Correctible Congenital Heart Disease.** Dr. Gordon S. Myers.

7:25–7:50 p.m. **Recognition of Correctible Congenital Malformations of the Gastrointestinal Tract.** Dr. Orvar Swenson.

8:00–8:25 p.m. **Problems of Adolescence in Girls.** Dr. Janet McArthur.

8:25–8:50 p.m. **Problems of Adolescence in Boys.** Dr. J. Roswell Gallagher.

8:50–9:00 p.m. **Discussion.**

Wednesday, April 30. THE DIAGNOSTIC AND THERAPEUTIC APPLICATIONS OF RADIOACTIVE ISOTOPES. Chairmen: Drs. Shields Warren and Charles L. Dunham.

4:00–4:10 p.m. **Introduction:** Dr. Shields Warren.

4:10–4:30 p.m. **The Nature of Radioactive Isotopes and the Biologic Effects of Their Radiations.** Dr. Sanborn C. Brown.

4:30–4:50 p.m. **Therapeutic Applications of Radiogold, Radiocobalt and Other Mechanically Positioned Isotopes in the Treatment of Cancer.** Dr. Marshall Brucer.

4:50–5:10 p.m. **The Treatment of Leukemia and Polycythemia Vera with Radioactive Phosphorus.** Dr. Charles L. Dunham.

5:10–5:30 p.m. **The Diagnosis and Treatment of Thyroid Diseases with Radioactive Iodine.** Dr. Belton A. Burrows.

5:30–5:50 p.m. **Localization of Tumors with Radioactive Isotopes.** Dr. William H. Sweet.

5:50–6:00 p.m. **Discussion.**

THE MATTER OF DUES

Various confusions seem to have arisen in regard to the payment of bills for dues to both the Massachusetts Medical Society and the American Medical Association.

The facts of the matter, as stated on the bills that have been sent out, are that each fellow of the Society owes to it $35.00 for his annual Massachusetts Medical Society dues, payable before March 1 of the current year. These dues include a subscription to the *New England Journal of Medicine*.

He also owes to the American Medical Association dues of $25.00, payable to that organization, which include a subscription to the *Journal of the American Medical Association.*

Thus two checks and two only are required, one for $35.00 payable to the Massachusetts Medical Society and one for $25.00 payable to the American Medical Association. Both are sent to the headquarters of the Massachusetts Medical Society, 22 Fenway, Boston, which collects for the American Medical Association and transmits to that organization.

The confusion has developed partly because the bills were sent separately instead of together, as originally planned, and partly because the second mailing, containing the single American Medical Association bill, contained also a red-printed slip that was originally intended to be sent in the same envelope with both bills, explaining the two payments. As a result, a considerable number of fellows who had already paid their Massachusetts Medical Society bill, their eyes attracted, no doubt, by the color of this slip, sent in two checks when paying the second bill (for the American Medical Association), thus paying twice for their Massachusetts Medical Society fellowship.

There is also some perturbation among a number of youthful fellows over seventy years of age — the American Medical Association age for voluntary retirement — who have been sent no bills for American Medical Association dues and have thus had their active membership in the Association either canceled because of nonpayment or placed in jeopardy, against their wishes.

They should have been billed each year as long as they wished to retain active membership, since it is specifically stated on the American Medical Association bill that members over seventy years of age are exempt from payment *on request.*

CORRESPONDENCE

THE PHYSICIAN AND POLITICS

To the Editor: It is obvious to many physicians that the medical profession is becoming circumscribed in its thinking on community problems. By this I mean not only the local community but the social and political problems of the community at large on a national level. There was a time when the physician was courageous enough to take a stand on inequities in government, believing that the high esteem in which the profession was held would spare him any personal besmirching.

The physician can no longer depend on this character protection, but the need still exists for his contribution to the political welfare of the community.

Doctors, particularly in the New England area, have tended to avoid political commitments, not through disinterest but through fear of unwholesome associations. The time has come, however, for the physician to make his contribution not only at the polls but also by seeking elective office and thus reflecting his knowledge of social and economic needs in the legislative bodies of this country. For this purpose he is ideally suited by virtue of his training to think objectively and sympathetically, and by virtue of his experience in human relations to view motives in their true light.

This letter is a plea to capable members of our profession to seek such office on a national as well as a local level, and for others to encourage them in this apparently thankless but vital task.

WILLIAM H. CHASEN, M.D.

Quincy, Massachusetts

SUSPENSION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held March 20, 1952, it was voted that the registration of Dr. Thomas P. Beatty, of South Boston, be suspended because of ill health.

ROBERT C. COCHRANE, M.D., *Secretary*

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held on March 20, 1952, it was voted that the registration of Dr. Robert B. Bigelow of South Lincoln, Massachusetts, be suspended because of ill health.

ROBERT C. COCHRANE, M.D., *Secretary*

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Tobacco and the Cardiovascular System: The effects of smoking and of nicotine on normal persons. By Grace M. Roth, Ph.D., associate professor of experimental medicine, Mayo Foundation for Medical Education and Research and Graduate School, University of Minnesota, and consultant, Section on Physiology, Mayo Clinic, Rochester, Minnesota. 8°, cloth, 66 pp., with 8 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $2.25. (Publication Number 100, American Lecture Series.)

This small monograph on a timely subject is well written and shows the results of extensive reading of the literature on the subject. A bibliography of 72 titles is appended to the text, and there is a good index.

Bionome Psychotherapie: Ein grundsätzlicher Versuch. By Prof. J. H. Schultz, Nervenärzt, Berlin. 8°, cloth, 186 pp., with 2 illustrations. Stuttgart: Georg Thieme, 1951. Ganzleinen DM 11.70. Distributed by Grune and Stratton, Incorporated, New York.

The text is divided into four major portions, on psychotherapy, life and the mind, the organism, vital circle and the mind, and the nature of neurosis. There are indexes of authors and subjects and the monograph is well printed.

NOTICES

AMERICAN COLLEGE HEALTH ASSOCIATION

The thirtieth annual meeting of the American College Health Association will be held at the Copley Plaza Hotel, Boston, May 1-3. Further information may be obtained from Dana L. Farnsworth, M.D., Massachusetts Institute of Technology, Cambridge, Massachusetts.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association announces the following programs to complete its Evening Lecture Series for 1951–1952:

May 6. "An Introduction to Vector Electrocardiography," by Dr. R. P. Grant, surgeon, U. S. Public Health Service, National Heart Institute. Discussers: Drs. Conger Williams and Harold Levine.

May 9. "The Nature of the Electrocardiographic Changes in Coronary Occlusion" (illustrated by high-speed motion picture film), by Dr. Myron Prinzmetal, associate professor of medicine, University of California School of Medicine. Discussers: Drs. David Littmann and Paul M. Zoll.

May 15. "Treatment of Epilepsy" (illustrated by the film *Seizure*), by Dr. W. G. Lennox, associate professor of neurology, Harvard Medical School. Discussers: Drs. R. S. Schwab and Derek E. Denny-Brown.

May 20. "The Respiratory and Metabolic Aspects of Acid-Base Control during Anesthesia," by Dr. Emanuel M. Papper, professor of anesthesiology, Columbia University College of Physicians and Surgeons. Discussers: Drs. H. K. Beecher and Sidney C. Wiggin.

May 27. "Some Aspects of the Pathogenesis of Essential Hypertension," by Dr. Ephraim Shorr, associate professor of medicine, Cornell University Medical College. Discussers: Drs. Reginald H. Smithwick and Lewis Dexter.

May 29. "Pulmonary Air Cysts: Some Diagnostic, Functional and Therapeutic Considerations," by Dr. K. Albert Harden, associate professor of medicine, Howard University College of Medicine. Discussers: Drs. Theodore L. Badger and Francis M. Woods.

June 3. "Pulmonary Function Tests," by Dr. Julius H. Comroe, professor of physiology and pharmacology, University of Pennsylvania Graduate School of Medicine. Discussers: Drs. J. L. Whittenberger, Edward Gaensler and Maurice Segal.

These programs are held at 7 p.m. in the New Cheever Amphitheatre of the Dowling Building of Boston City Hospital. All interested persons are invited to attend.

CHILDREN'S MEDICAL CENTER

A lecture will be presented by the Department of Pathology, Harvard Medical School at The Children's Hospital, and The Children's Cancer Research Foundation at 4:30 p.m. on April 29 in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston.

Dr. G. Burroughs Mider, professor of cancer research at the University of Rochester, will speak on "Tumor-Host Relations."

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The annual meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, on May 13 at 7:30 p.m. The business meeting (election of officers for 1952–1953) will take place from 7:30 to 8:00 p.m. At the scientific meeting (8:00-9:00 p.m), Dr. Harris Isbell will discuss "Addiction and Its Clinical Manifestations in Management."

SPRINGFIELD ACADEMY OF MEDICINE

The next meeting of the Springfield Academy of Medicine will be held on May 13. Dr. Richard Freyberg will speak on "Recent Trends in the Treatment of Arthritis."

HAMPDEN DISTRICT MEDICAL SOCIETY

The Annual Meeting of Hampden District Medical Society will be held on April 22, at 6:30 p.m., at the new Soldiers' Home in Holyoke.

SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of May is as follows:

May 3
10–11 a.m. Surgical Grand Rounds.
11 a.m.–12 m. Medical-Surgical Clinic. Staff Conference Room.

May 7
11 a.m.–12 m. Psychosomatic Medicine — Group Therapy. Drs. Calvert Stein and J. Graham Bruce. Board Room.

May 8
12:15 p.m. Staff Meeting. Staff Room.

May 10
10–11 a.m. Surgical Grand Rounds.
11 a.m.–12 m. Clinicopathological Conference. Staff Conference Room.

May 14
11 a.m.–12 m. Psychosomatic Medicine Conference (with sound film) on "Problems in Rheumatic Arthritis." Staff Conference Room. Dr. J. Graham Bruce.

May 17
10–11 a.m. Surgical Grand Rounds.
11 a.m.–12 m. Medical Death Review. Staff Conference Room.
1:30 p.m. New England Pathological Society Meeting. Staff Conference Room.

May 20
8:30 p.m. Guest Speaker Conference in the Staff Conference Room. "Intracardiac Surgery and Physiology," by Dr. John Gordon Scannell, assistant surgeon, Massachusetts General Hospital, and instructor in surgery, Harvard Medical School.
11 a.m.–12 m. Psychosomatic Medicine — Group Therapy. Drs. Calvert Stein and J. Graham Bruce. Board Room.

May 24
10–11 a.m. Surgical Grand Rounds.
11 a.m.–12 m. Surgical Death Review. Staff Conference Room.

May 28
11 a.m.–12 m. Psychosomatic Medicine — Group Therapy. Drs. Calvert Stein and J. Graham Bruce. Board Room.

May 31: Holiday weekend; no conferences.

DAVID ANDERSON-BERRY PRIZE (1953)

A David Anderson-Berry Silver-gilt medal, together with a sum of money amounting to about £100, will be awarded in 1953 by the Royal Society of Edinburgh to the person who, in the opinion of the Council, has recently produced the best work on the therapeutic effect of x-rays on human diseases. Applications for this prize may be based on both published and unpublished work and should be accompanied by copies of relevant papers. Applications must be in the hands of the General Secretary, Royal Society of Edinburgh, 22 George Street, Edinburgh, 2, by March 31, 1953.

SOCIETY MEETINGS AND CONFERENCES

APRIL 17–19. Boston Lying-in Hospital and Children's Hospital Postgraduate Course in Obstetrics and Pediatrics. Page 433, issue of March 13.

APRIL 21–25. American College of Physicians. Page 522, issue of March 27.

APRIL 21–25. Cancer Seminar. Page 114, issue of January 17.

APRIL 22. Norfolk District Medical Society. Page 710, issue of November 1.

APRIL 22. Hampden District Medical Society. Notice above.

APRIL 22. Harvard Medical Society. Page 595, issue of April 10.

APRIL 22, 25 AND 29. Boston City Hospital House Officers' Association. Page 459, issue of April 3.

APRIL 23. Massachusetts Academy of General Practice. Springfield. Page 560, issue of April 3.

APRIL 23. New England Obstetrical and Gynecological Society (Spring Meeting). Hartford, Connecticut.

APRIL 23–30. Springfield Hospital. Page 433, issue of March 13.

APRIL 23–30. Postgraduate Lecture Course. Page 633.

APRIL 25 AND 26. Texas Medical Center. Page 354, issue of February 28.

APRIL 26. Boston City Hospital Alumni Association. Page 476, issue of March 20.

APRIL 26. Alumni Association of Long Island College of Medicine. Page 434, issue of March 13.

APRIL 29. Children's Medical Center. Notice above.

APRIL 30. Middlesex West District Medical Society. Hotel Kendall, Framingham. 6:15 p.m.

MAY 1–3. American College Health Association. Page 634.

MAY 3. New England Society of Anesthesiologists. Page 595, issue of April 10.

MAY 3. Boston University School of Medicine Alumni Association. Page 560, issue of April 3.

MAY 3. Annual Meeting. Massachusetts Association of Medical Technologists, Inc. Page 433, issue of March 13.

MAY 3–31. Springfield Hospital. Notice above.

MAY 6–JUNE 3. Boston City Hospital House Officers' Association. Page 634.

MAY 7. Massachusetts Society of Examining Physicians. Page 595, issue of April 10.

MAY 8. The Choice of Patients for the Surgical Treatment of Hypertension. Dr. James A. Evans. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

MAY 8–10. American Neurological Association. Page 559, issue of April 3.

MAY 10. Boston Dispensary Proctologic Session. Page 433, issue of March 13.

MAY 10 AND 11. American Electroencephalographic Society. Page 390, issue of March 6.

MAY 11–17. Pan-American Convention of Gastroenterology. Page 434, issue of March 13.

MAY 13. New England Society of Anesthesiologists. Page 635.

MAY 13. Springfield Academy of Medicine. Page 635.

MAY 15–17. American College of Surgeons. Page 596, issue of April 10.

MAY 19–22. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 19–23. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

MAY 21 AND 22. Venereal-Disease Seminar. Page 559, issue of April 3.

MAY 22–24. American Academy of Pediatrics. Page 522, issue of March 27.

MAY 26–28. Minnesota State Medical Association. Annual Meeting. Page 316, issue of February 21.

MAY 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.

MAY 29–31. American Academy of Dental Medicine. Page 476, issue of March 20.

JUNE 5–8. American College of Chest Physicians. Page 280, issue of February 14.

JUNE 18–20. Massachusetts Public Health Conference. Amherst.

JUNE 19–21. American Association of Genito-Urinary Surgeons. Page 434, issue of March 13.

JUNE 22–26. American Society of Medical Technologists. Twentieth Annual Convention. Portland, Oregon.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–11. International Congress of Dietetics. Page 434, issue of March 13.

JULY 7–12. International Diabetes Federation. Page 316, issue of February 21.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

JULY 24–26. Conference on Aging. Page 559, issue of April 3.

AUGUST 25–29. American Congress of Physical Medicine. Page 476, issue of March 20.

AUGUST 31–SEPTEMBER 6. Interamerican Congress of Cardiology. Page 522, issue of March 27.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies. Mount Washington Hotel, Bretton Woods, New Hampshire.

OCTOBER 28–30. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

NOVEMBER 3–7 AND 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

JULY, 1953. International Congress on Medical Librarianship. Page 316, issue of February 21.

District Medical Societies

HAMPDEN

APRIL 22. Soldiers' Home, Holyoke.

HAMPSHIRE

MAY 7. Annual Meeting. Jones Library, Amherst.

MIDDLESEX SOUTH

APRIL 30. Hotel Continental, Cambridge.

MIDDLESEX WEST

APRIL 30. 6:15 p.m. Hotel Kendall, Framingham.

NORFOLK

APRIL 22. Boston Medical Library.
MAY 7. Place to be announced.

Calendar of Boston District for the Week Beginning Thursday, April 24

THURSDAY, APRIL 24

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Grand Rounds. House of the Good Samaritan.

12:00 m.–1:00 p.m. Weekly guest speaker Dr. A. Stone Freedberg. Stearns Auditorium, New England Center Hospital.

*4:00–5:00 p.m. Medical Division Lecture. Mount Auburn Hospital, Cambridge.

4:00 p.m. Recent Results in the Application of the Freeze-Drying Technique to Autoradiography. Dr. Margaret Holt. Cancer Research Institute Auditorium, New England Deaconess Hospital.

4:00 p.m. Effect of Cortisone on Structure and Nucleic Acid Content of Lymph Nodes. Dr. E. H. Kass. Amphitheatre D, Harvard Medical School.

FRIDAY, APRIL 25

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.

*11:00 a.m.–12:00 m. Pediatrics. Woolson II, Mount Auburn Hospital, Cambridge.

*12:00 m.–1:30 p.m. Surgical Pathological Conference. Pratt Diagnostic Clinic, New England Center Hospital.

2:00–4:00 p.m. Arthritis Conference. Stearns Auditorium, New England Center Hospital.

2:30–3:30 p.m. Pulmonary Conference. Stearns Auditorium, New England Center Hospital.

4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.

4:30 p.m. Public Health Forum: The British National Health Services: Its achievements and its weaknesses. Dr. Allen Daley, Medical Officer of Health, London County Council. Harvard School of Public Health, Jimmy Building Auditorium, 35 Binney Street.

7:00 p.m. Boston City Hospital House Officers' Association. Cheever Amphitheatre, Dowling Building, Boston City Hospital.

SATURDAY, APRIL 26

8:30 a.m.–1:00 p.m. Boston City Hospital Alumni Association.

10:30 a.m.–12:00 m. Electrocardiogram Interpretation. Massachusetts General Hospital.

*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, APRIL 28

8:30 a.m. Eye Clinical Conference. Out Patient Department, Massachusetts Eye and Ear Infirmary.

8:30 a.m. Eye Clinico-Pathological Conference. Out Patient Department, Massachusetts Eye and Ear Infirmary.

8:30–9:30 a.m. Surgical Clinic by entire staff. Cheever Amphitheatre, Dowling Building, Boston City Hospital.

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street. Dr. Cleaveland Floyd in charge.

*12:00 m.–1:00 p.m. Hematology Conference. Dr. Dameshek. Stearns Auditorium, New England Center Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheatre, Peter Bent Brigham Hospital.

2:00–8:30 p.m. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.

*3:00–4:00 p.m. Gynecology Rounds. Mount Auburn Hospital, Cambridge.

5:00 p.m. Biological Chemistry and Biophysics Seminar: Studies on Adrenal Physiology in Rheumatic Fever. Dr. J. E. Warren. Bowditch Library, Harvard Medical School.

5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

7:00–9:00 p.m. Postgraduate Lecture Course. Boston Medical Library, 8 Fenway.

TUESDAY, APRIL 29

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:00 m.–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Pathological Conference. Mount Auburn Hospital, Cambridge.

4:30 p.m. Children's Medical Center. Auditorium, Jimmy Fund Building, 35 Binney Street.

*5:00–6:00 p.m. Surgical Lecture. Mount Auburn Hospital, Cambridge.

*7:00 p.m. Boston City Hospital House Officers' Association. Cheever Amphitheatre, Dowling Building, Boston City Hospital.

WEDNESDAY, APRIL 30

*11:00 a.m.–12:00 m. Medical Clinic (Children's Medical Center). Amphitheatre, Children's Hospital.

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

12:00 m.–1:00 p.m. Medical Conference: Gastroscopic and Histological Examinations of Gastric Lesions. Drs. Emmanuel Deutsch and H. E. MacMahon. Pratt Diagnostic Clinic, New England Center Hospital.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheatre, Peter Bent Brigham Hospital.

12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheatre, New England Deaconess Hospital.

*2:00–3:00 p.m. Combined Clinic of all services (Children's Medical Center). Amphitheatre, Children's Hospital.

4:00–6:00 p.m. Postgraduate Lecture Course. Boston Medical Library, 8 Fenway.

8:15 p.m. Psychological Aspects of Pediatrics. Dr. T. Berry Brazelton. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*Open to the medical profession.